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Targeting tumors with LIGHT to generate metastasis-clearing immunity

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Abstract

Metastastic diseases cause the majority of morbidity and mortality of cancer patients. Established tumors form both physical and immunological barriers to limit immune detection and destruction. Current immunotherapy of vaccination and adoptive transfer shows limited effect at least in part due to the existing barriers in the tumors and depending on the knowledge of tumor antigens. Tumor necrosis factor superfamily member 14 (TNFSF14) LIGHT interacts with stromal cells, dendritic cells, NK cells, naïve and activated T cells and tumor cells inside the tumor tissues via its two functional receptors, HVEM and lymphotoxin β receptor (LTβR). Targeting tumor tissues with LIGHT leads to augmentation of priming, recruitment, and retention of effector cells at tumor sites, directly or indirectly, to induce strong anti-tumor immunity to inhibit the growth of primary tumors as well as eradicate metastases. Intratumor treatment would break tumor barriers and allow strong immunity against various tumors without defining tumor antigens. This review summarizes recent findings to support that LIGHT is a promising candidate for an effective cancer immunotherapy.

Keywords

tumor; metastasis; immunotherapy; TNF Superfamily; gene therapy; T cells

1. INTRODUCTION

Many cancers are antigenic and can be recognized by T cells[1]. However, mere recognition by adaptive immunity is insufficient to cause the regression of cancers. An effective anti-tumor immune response depends not only on the presence of tumor-reactive lymphocytes in the tumor-bearing host, but also requires at least three additional conditions. First, naïve tumor-specific T cells must be primed in a proper environment for their expansion and maturation to effector cells. Second, the effector T cells must be able to reach the tumor site. Finally, lymphocytes in the tumor must be able to appropriately execute effector functions to destroy cancer cells. The goal of cancer immunotherapy is to overcome tumor-associated immune-suppressive mechanisms at each of these steps, in order to induce potent anti-tumor immunity.

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LIGHT [an acronym for homologous to ***l***ymphotoxins, shows ***i***nducible expression, and competes with herpes simplex virus ***g***lycoprotein D for ***h***erpesvirus entry mediator (HVEM), a receptor expressed by ***T*** lymphocytes] is a tumor necrosis factor (TNF) superfamily (TNFSF) member that is naturally expressed on immature dendritic cells (DCs) and activated T cells [2,3]. LIGHT uniquely binds to two functional receptors, HVEM and lymphotoxin β receptor (LTβR) [2,4], which are TNF receptor superfamily members (TNFRSF) that have distinct expression patterns. HVEM is broadly expressed on hematopoietic cells including T cells, natural killer (NK) cells, and monocytes [5,6]. Conversely, LTβR is mainly expressed on non-hematopoietic cells such as stromal cells [7] and some monocyte cell lines [8]. Stimulation *via* LIGHT leads to augmentation of priming, recruitment, and retention of effector cells at tumor sites, directly or indirectly, to induce strong anti-tumor immunity. This review will discuss recent findings regarding the possible mechanisms of how LIGHT provokes anti-tumor immunity at multiple stages of T cell responses, which puts LIGHT at a unique position to be a promising candidate for cancer immunotherapy.

2. PRIMING OF TUMOR-SPECIFIC T CELLS

2.1. Hindrance of priming by tumor stroma

All solid tumors are composed of malignant cells that are embedded in a stroma containing a mixed population of nonmalignant cells: bone marrow-derived myeloid cells, non-bone marrow-derived endothelium, fibroblasts, and cells of the vasculature. Experimental evidence has demonstrated that the non-antigenic stroma may present an important immunological barrier that prevents immune recognition and destruction of tumors [9–11]. More recently, a more physiological model was developed to analyze spontaneously arising primary tumors, which originated from single transformed precursor cells embedded in nonmalignant stroma. Nascent primary solid tumors, even when highly antigenic *in vitro*, failed to prime antigen-specific T cells during the initial stages *in vivo* [12]. This observation is in concordance with other experiments that also suggest that tumor stroma may act as a barrier to antigen presentation and immune recognition [13,14].

Anti-tumor immune response is initiated when tumor antigens are transported out of the tumor to the draining lymph nodes (DLN) [15], either perched atop an antigen-presenting cell (APC) for indirect presentation [16] or by tumor cells themselves for direct presentation [11]. However, tumor stroma may hinder T cell priming by sequestering antigenic tumor cells, thus preventing them from reaching the DLN to directly prime a T cell response [17]. In such an event, cross-presentation by professional APCs, often DCs, from the tumor tissues becomes a major pathway for naïve T cells to be primed tumor antigens. In addition, the stroma matrix may directly interfere with T cell priming by reducing the degree of available antigens. The extracellular matrix proteins can directly bind to tumor antigens [18], while the stromal endothelium and fibroblasts may compete with DCs for antigen uptake [19]. Thus, cancer cells embedded in non-malignant stroma may be ignored [11] when tumor antigens are not expressed at a high level, like in most human cancers. In order to allow priming of tumor-specific T cells and generate strong anti-tumor immunity, it is critical to: 1) penetrate and bypass the non-antigenic stroma, 2) promote cross-presentation by DCs, and 3) release more tumor antigen.

2.2. LIGHT creates lymphoid-like tissues inside the tumor to improve priming

Although cancer cells express mutant or unique proteins that the immune system can recognize as foreign [20], malignant cells are surrounded by non-malignant stroma which forms a complex multicellular “organ” resembling self. The induction of immunity against normal, non-mutated differentiation antigens expressed by tumors resembles autoimmunity. Comparable to anti-tumor immunity, it is often observed in murine autoimmune models that the presence of autoreactive cells alone is not sufficient to cause tissue destruction [21]. It has

been reported recently that the organized tertiary lymphoid structure (TLS) is necessary and sufficient to induce autoimmune destruction of pancreatic islets [22]. Indeed, *de novo* organization of TLS is known to precede the development of a number of human autoimmune diseases [23,24]. These observations suggest that lymphoid neogenesis within the target tissue may have a critical role in initiating and maintaining immune responses against persistent antigens. TLS are not supplied by afferent lymph vessels and are not encapsulated, which implies that they are directly exposed to signals such as stimulating antigens and cytokines from the environment. This incomplete development of TLS could potentially result in unrestricted access of DCs and lymphocytes to the TLS, favoring immune activation. Although disruption of established TLS or prevention of TLS formation may be advantageous in treating autoimmune diseases, initiation of intra-tumor lymphoid structure formation may facilitate the eradication of tumors. Considering the T cell repertoire may be less responsive against the self-antigens involved in autoimmunity than against the unique antigens involved in tumor immunity, the destruction of cancers would be further facilitated by the availability of high-affinity T lymphocytes in the presence of TLS inside the tumor.

Clues to understanding the signals that lead to TLS formation come from the study of the signaling pathways involved in secondary lymphoid tissue organogenesis. Studies in mutant mice and blocking experiments have identified a key requirement for TNF-family members, mainly lymphotoxin α1β2 (LTα1β2), and to some extent TNF, in the development and organization of lymph nodes and spleen microarchitecture[25–28]. Binding of LTα1β2 and TNF to their respective receptors, LTβR and TNFR1, induces the expression of chemokines and adhesion molecules, which directly mediate lymphocyte migration and homing[29]. The first evidence that the generation of TLS could involve the same signaling pathways that regulate lymphoid organogenesis came from studies of transgenic mice [24], in which the ectopic expression of LTα and LTβ in pancreatic islets induced the formation of in-situ TLS [30–33]. Extrapolating from this earlier experiment, stimulation of LTβR or TNFR expressed by tumor stromal cells may promote the formation of lymphoid-like structures inside the tumor tissues, which in turn may facilitate tumor destruction. Systemic TNFR signaling is of course too toxic, as evidenced by other systemic TNF treatments [34]. Soluble LTα can signal through the TNFR resulting in the upregulation of chemokines. To avoid systemic toxic effects, recombinant LTα has been conjugated with tumor-specific antibody to be delivered specifically to the tumor tissue [35]. Targeting of recombinant LTα to the tumor elicits an efficient immune response associated with the induction of peripheral lymphoid-like tissue containing L-selectin^{+} naïve T cells and MHC class II^{+} antigen-presenting cells[35]. Secondary lymphoid tissue chemokine (SLC or CCL21) is among the chemokines controlled by LTβR and TNFR signaling [29]. It is normally expressed in high endothelial venules and in T-cell zones of the spleen and lymph nodes and strongly attracts naive T cells and DCs [36]. The expression of CCL21 inside the tumor resulted in a substantial, sustained influx of T cells within the mass as well as retention of DCs at the tumor site. By recruiting T cells and DCs, CCL21 in the tumor may lead to extranodal priming and inhibition of tumor growth [37].

Similar to LTα1β2, LIGHT also activates LTβR. Our data indicate that the interactions between LIGHT and LTβR restore lymphoid structures in the spleen of LTα$^{-/-}$ mice [38]. *In vivo* data demonstrate that LIGHT mediates development of a microenvironment sufficient to break immunological tolerance to self antigens. First, ectopic expression of LIGHT in the pancreatic islets resulted in the formation of lymphoid-like structures and was necessary and sufficient for pancreatic islet destruction [22]. In addition, sustained expression of LIGHT on T cells leads to their activation, migration into peripheral tissues, and the establishment of lymphoid-like structures *in situ* [38,39]. LIGHT also acts as a strong costimulatory molecule for T cell activation, possibly by binding to HVEM on T cells [3]. Therefore, LIGHT, delivered inside the tumor, is an ideal candidate for creating TLS to recruit more T cells and subsequently expand antigen-specific ones inside the tumor. In addition to the cross-presentation pathway,

tumor-reactive T cells can be activated *via* direct presentation in the presence of antigens and costimulation. Indeed, LIGHT ectopically expressed in the tumor can effectively recruit and activate naïve T cells. The expression of LIGHT in the tumor environment induces an infiltration of naive T lymphocytes that correlates with an upregulation of both chemokine production and expression of adhesion molecules inside tumors [40]. Activation and expansion of these infiltrating T cells, likely *via* both cross- and direct-presentation pathways, leads to the rejection of established, highly progressive tumors at local and distal sites[40]. These experiments demonstrate that introduction of the lymphoid-like structure into the tumor stroma can be highly effective in enhancing antigen recognition and may be a potent strategy for cancer immunotherapy.

The ability to directly prime naïve T cells within the tumor itself permits several advantages. First, the efficiency and specificity of priming will be increased due to the higher tumor antigen load *in situ* relative to that collected in the draining lymphoid tissues [16] and second, a broader repertoire of tumor-specific naïve T cells is recruited to the site of tumor antigens, leading to a more comprehensive response [35,41]. It has been shown that some tumor antigens may not be efficiently cross-presented due to the antigen bias in T cell cross-priming [42]. In these instances, we have demonstrated in our experimental system using the tumor cell line Ag104L^{d}-LIGHT that certain antigens are presented to and activate naïve T cells within the tumor *via* a direct presentation mechanism[40,43]. The same tumor would have been otherwise overlooked by the host immune response had it relied solely on draining lymphoid tissues and cross-presentation. Furthermore, no additional migration steps are required for CTL to reach the site of effector function, which leads to the appearance of activated tumor-reactive T cells in a short period of time. Finally, T cell responses may react more readily to the shifting tumor antigen expression profile *in situ*. T cell stimulation in the absence of costimulation can induce anergy and apoptosis of antigen-specific T cells [44–46]. Costimulation has also been shown to greatly enhance tumor-specific T cell function during the effector phase [15]. Earlier studies show that LIGHT provides CD28-independent costimulation [3], which may be essential for the selective and effective activation, expansion and maintenance of tumor-specific T cells among infiltrating naïve T cells in Ag104L^{d}-LIGHT tumors. By working as both a costimulatory molecule and generating lymphoid-like milieus through the induction of proper chemokines and adhesion molecules, LIGHT is a potent molecule capable of generating better immune responses against established tumor. Interestingly, a recent study showed that LIGHT is constitutively expressed in some human melanoma cells and tumor-derived microvesicles, and tumors that expressed LIGHT were associated with significantly increased lymphocytic infiltration [47].

2.3. LIGHT regulates DCs at the tumor site to promote priming

Since DCs are the major APCs for antigen presentation, increased numbers of DCs may contribute to the enhanced priming of lymphocytes leading to improved anti-tumor immunity. LTβR signaling is critical for maintenance of a normal number and position of DCs in the spleen[48], which can be attributed to two major roles LTβR signaling plays in regulating of DCs.

Upon activation and maturation, DCs migrate to the T cell zones of lymphoid tissues responding to a chemokine gradient, where they initiate immune responses or induce tolerance [49–51]. This migratory process of DCs is dependent upon their ability to express chemokine receptor CCR7 [52,53]. The ligands of CCR7 include CCL21 and CCL19, which are expressed by lymphatic endothelium and stromal cells [36]. LTβR signaling controls CCL21 and CCL19 expression in the spleen, which may be critical for the migration and/or positioning of DCs in the spleen [29]. Thus, the LTβR signaling-induced chemokine microenvironment on the stroma is critical for the recruitment of DCs.

In addition, more recent studies show that the lack of direct LTβR signaling on DCs is associated with the reduction of the number of DCs in the spleen, independent of the chemokine gradients. These studies suggest that DC proliferation is an important pathway for locally maintaining these cells in the steady state, and LTβR signaling on the DCs is critical for their proliferation [54,55]. More importantly, LIGHT stimulation dramatically increases the number of DCs in a LTβR-dependent fashion, and intratumor expression of LIGHT can dramatically expand DCs *in situ*. This increase of DCs possibly contributes to the enhancement of tumor immunity in the LIGHT-mediated tumor environment, which is consistent with the one observed with inoculation of DCs into tumor tissues [55]. Therefore, LTβR signaling regulates DCs for their homeostasis during physiological and pathological conditions, and increased LIGHT- LTβR interaction could stimulate DC expansion for T cell-mediated anti-tumor immunity.

Besides quantity and localization, when antigen is cross-presented to T cells in the DLN by DCs, whether tolerance or immunity is induced depends heavily on the maturation state of the DCs presenting the antigen [56,57]. Under normal, steady-state conditions, immature DCs cross-present antigens to induce peripheral tolerance [58]. Tolerance may be maintained at the level of T cell expansion through defective signaling pathways [59]. While steady-state conditions lead to tolerance, Signals that promote DC maturation lead to immunity [60–62]. Several characteristics that mature DCs possess including increased presentation of peptide-MHC complexes and induced expression of co-stimulatory molecules like CD80 and CD86, cytokines and chemokines are critical for the initiation and enhancement of immune responses. Thus, tumor antigens that are cross-presented by mature DCs are more likely to induce tumor immunity. A recent study has shown that global LTβR signaling is required for maximal expression of CD86 on Ag-bearing DC and for efficient priming of T cells, and that the LTβR signaling on the DCs is essential to condition them for T cell priming [63]. Moreover, the DCs that become non-functional in the absence of CD40L, an important signal for DC maturation, on Ag-specific T cells can be overcome by stimulating LTβR [63]. This observation is consistent with previous findings that LIGHT can cooperate with CD40L to induce the maturation of monocyte-derived DCs [64]. Thus, we propose that LIGHT delivered into the tumor environment can stimulate LTβR signaling to promote full conditioning of DCs during the priming of anti-tumor immune response.

2.4. Tumor cell apoptosis induced by LIGHT promotes immune recognition

Cancers often express low levels of antigens. Increasing the release of antigen from the tumor cells may break immunological ignorance. For example, apoptosis of cancer cells induced by chemotherapeutic agents or radiation releases antigen, enhancing the cross-priming of T cells [65,66]. LIGHT has been shown to signal *via* LTβR and/or HVEM expressed on the tumor cells to induce apoptosis of the tumor cells, especially in the presence of interferon-γ [4,5, 67]. Using a xenograft tumor model in which human breast cancer cells were inoculated to athymic nude mice, LIGHT directly inhibited tumor growth by causing apoptosis in the absence of T cells [68]. We have shown in multiple tumor models that LIGHT mediated tumor regression is dependent on T cells, especially $CD8^+$ T cells [40,69]. However, our results do not exclude the possibility that the induction of apoptosis of tumor cells by LIGHT also causes increased release of tumor antigen, leading to enhanced priming and T cell-dependent anti-tumor immunity. In addition, it would be interesting to investigate if high levels of IFN-γ in the LIGHT-mediated microenvironment [40], due to an enhanced T cell-mediated immune response, contributes to direct inhibition of tumor growth by way of LTβR signaling-induced apoptosis. In turn, the release of tumor antigen could result in a better T cell response and more IFN-γ production. It is possible that this positive loop is one of the important mechanisms of how LIGHT induces powerful anti-tumor immunity against tumors that express LTβR and/or HVEM.

3. EFFECTOR T CELLS AT THE TUMOR SITE

3.1. The immunosuppressive environment inside tumors

Even with immune recognition of cancer, which can occur in cancer patients and is evidenced by the frequent observation of T cell infiltration into cancerous tissues [70–73], it is rare for such tumor infiltrating T cells to induce the spontaneous rejection of established tumors. Accumulating evidence indicates that the tumor environment contains cells and cytokines that actively suppress primed effector T cells [74,75]. High concentrations of transforming growth factor-β (TGF-β), produced by cancer cells or stromal cells, are frequently found in solid tumors and interfere with effective immune rejection of tumor [76]. TGF-β is a cytokine essential for the generation and survival of $CD4^+CD25^+$ regulatory T cells (Treg) [77,78], which may themselves produce TGF-β and IL-10 to reinforce the immune suppressive loop that exists in the tumor environment. While active TGF-β does not inhibit lysis by CTLs, it can inhibit maturation of T cells to that effector state [79]. This explains, at least in part, how $CD8^+$ T cells resistant to TGF-β1 can mediate tumor rejection [80].

Highly antigenic tumors may fail to regress in the host due to an accumulation of regulatory T cells within the tumor microenvironment [81]. These $CD4^+CD25^+$ regulatory T cells seem not only to inhibit developing tumor-specific $CD8^+$ T cells from gaining full effector function, but can even block transferred, fully activated tumor-specific T cells from mediating tumor rejection *in vivo* [82]. We have demonstrated that the local intratumoral depletion of these regulatory T cells changes the cytokine milieu of the tumor, unmasks the immunogenicity of tumor, and reverses CTL tolerization, leading to the rapid rejection of well-established tumors [81]. Our data support the idea that regulatory T cells inhibit not only the early priming events, but also the effector function of T cells inside tumors, which is supported by a recent study [82].

3.2. LIGHT sustains effector T cell functions at the tumor site

It is still not well understood if and how a $CD8^+$ T cell that has been exposed to the immune suppressive environment inside the tumor converts back to a fully functional effector cell. The LIGHT-mediated tumor environment contains fully functional $CD8^+$ effector T cells [40]. This might be in part contributed to the ability of LIGHT to act as a strong costimulatory molecule for T cell activation, expansion and cytokine production, possibly by binding to HVEM on T cells [2,3,68]. This was initially demonstrated by experiments in which immobilized recombinant LIGHT promoted T cell proliferation in the presence of anti-CD3 [5]. Reagents that blocked HVEM, like anti-HVEM antibody [6] or HVEM-Ig [83], reduced T cell expansion and their cytokine production in the same setting. This is consistent with the later findings that $CD8^+$ T cell activation, expansion and CTL activity are defective in LIGHT-deficient mice [84–86]. It appears that endogenous LIGHT is critical for $CD8^+$ T cell activation *in vivo*. Beside its critical role in initiation of T cell activation, costimulation has also been shown to greatly enhance tumor-specific T cell function during the effector phase. It would be interesting to see if LIGHT stimulation is sufficient to convert tolerized $CD8^+$ T cell to functional effectors [15].

Besides its direct role on T cells, the additional role of LIGHT on natural killer (NK) cells may contribute to the promotion of effector T cell function for anti-tumor immunity. LIGHT is a critical ligand for activating NK cells to produce large amount of IFN-γ, possibly *via* HVEM expressed on the NK cells[87]. Activated NK cells facilitate the further activation of tumor-specific $CD8^+$ T cells in an IFN-γ–dependent manner at the tumor site. The expression of LIGHT inside tumors leads to an increase in number of NK cells in the tumor, possibly through either expansion or recruitment of NK cells[87]. It would be interesting to see if LIGHT-activated NK cells also mediate direct tumor suppression in other tumor models.

T cells activated by LIGHT–HVEM produce typical T-helper cell type 1 (Th1) cytokines including IFN-γ and GM-CSF [3,39]. Additional LIGHT stimulation can cause severe inflammation in non-lymphoid tissues, as demonstrated by murine models of constitutive expression of mouse [39] or human LIGHT [88] under a T cell promoter. We found that forced expression of LIGHT inside tumor tissues promoted a change of cytokine environment inside the tumor, possibly contributing to the generation of fully functional $CD8^+$ T cells and leading to the eradication of highly established tumors in mice [40]. The question remains as to whether LIGHT also modulates Treg, as well as $Gr\text{-}1^+$ $CD11b^+$ immature myeloid cells, which also have powerful immunosuppressive effects inside a tumor environment.

4. LIGHT RECRUITS AND SUSTAINS EFFECTOR T CELLS - Combination with current strategies for cancer immunotherapy

Active immunization and adoptive T cell transfer therapy are the main strategies used thus far for cancer immunotherapy. Both of these strategies are designed to overcome the deficiency in the priming of tumor antigen-specific T cells in the cancer-bearing hosts. Cancer vaccines rely on immunization of patients with antigenic peptides, proteins or DNA expressed by the tumor directly or delivered by DC or virus, etc. Despite relative simplicity and safety, vaccine treatments have shown very limited success [89]. Although the generation *in vivo* of antitumor T cells in vaccinated patients could be demonstrated by techniques such as tetramer or ELISpot assays [90–92], clinical responses observed from these trials were few [89]. This was consistent with the finding in murine models that the presence of even large numbers of antigen-specific T cells is insufficient to mediate tumor regression [14,93]. There are a multitude of explanations for this; for example, the relatively inadequate numbers or avidity of the immune cells, the inability of the tumor to recruit or activate quiescent or precursor lymphocytes, short-lived effector cells, tolerance mechanisms including the lack of costimulation, anergy, and active suppressive influences produced by the tumor environment. These obstacles must be overcome if cancer vaccines are to be effective in mediating cancer regression.

Adoptive transfer immune therapies, in which T cells are isolated from tumor or patients' peripheral blood, are expanded *in vitro* in a relatively tumor antigen-specific way for adoptive transfer[94], have been used in a small number of highly selected melanoma patients[95]. Although the prerequisite knowledge of the antigens and the potential inability to isolate or expand T cells against the tumor likely limit their application to only a minority of cancer patients, it has shown promise in some of the treated patients [95].

The LIGHT-mediated tumor environment can potentially work synergistically with active immunization and adoptive transfer therapy. Signaling by LTβR expressed by tumor stromal cells, not only promotes naïve T cell recruitment by CCL21, but also upregulates chemokines and adhesion molecules, such as IP-10 and Mig [40] to potentially attract activated T cells to tumor site. Adhesion molecules such as MAdCAM-1, which are essential for lymphocyte migration into peripheral tissues, are also upregulated in the LIGHT-mediated environment [40]. The LIGHT-mediated environment promotes the recruitment of activated T cells, augmented by immunization or adoptive transfer, and improves effector cell function to potentially enhance current strategies for cancer immunotherapy.

5. GENERATION OF CTL IN THE LIGHT-MEDIATED TUMOR ENVIRONMENT -------Treatment of metastases

Micrometastases can establish early in heterogeneous primary tumor development and seed distal sites prior to clinical detection [96]. Therefore, at the time of diagnosis many cancer patients already have microscopic metastases, an observation that has led to the development of post-surgical adjuvant therapy for patients with solid tumors. Despite advances in early

detection and modifications to treatment regimens, success has been limited and optimal treatment of metastatic disease continues to pose a major challenge in cancer therapy.

We have shown that expression of LIGHT in the tumor can lead to rejection not only at a local site but also at distal sites. To develop more clinically relevant approaches, adenovirus vectors that express LIGHT (Ad-LIGHT) have been constructed to deliver LIGHT into the tumor tissue. The advantages of the adenoviral delivery system are 1) high production of non-replicable virus; 2) activation of innate immunity; 3) an ability to express its carrying gene in non-dividing cells, and 4) ease of expression in most tumor cell lines. Administration of Ad-LIGHT into the tumor tissue leads to the complete rejection of an aggressive fibrosacoma $Ag104L^d$ and retards the growth of other tumors, such as melanoma B16, colon cancer MC38, and breast cancer 4T1 in mice [69]. The poorly immunogenic 4T1 mammary carcinoma closely mimics human breast cancer in its anatomical site, immunogenicity, growth characteristics, and more importantly, metastatic properties[97–99]. We have demonstrated in this model that generating immune responses in primary tumor tissues prior to surgical resection can produce tumor-specific effector T cells sufficient to eradicate distant metastases in a CD8-dependent fashion. Local treatment with Ad-LIGHT initiated priming of tumor-specific $CD8^+$ T cells directly in the primary tumor, with subsequent exit of CTLs which homed to distal tumors to elicit immune-mediated eradication of spontaneous metastases [69]. Recent study has also shown that attenuated Salmonella engineered to produce LIGHT inhibit primary tumor growth as well as dissemination of pulmonary metastases [100].

Conventional treatment such as surgical removal of tumor followed by radiation and chemotherapy may prevent effective immune recognition of cancers due to the loss of a major source of antigens, and damage to preexisting CTL by radiation and chemotherapy. An alternative strategy would be to utilize the primary tumor as the site of CTL priming prior to surgical resection. Delivery of LIGHT expression within the tumor environment recruits naïve T cells and generates tumor-specific CTLs that can survive and exit the microenvironment to patrol peripheral tissues and eradicate disseminated metastases.

5. CONCLUSIONS

Understanding the balance of anti-tumor effectors vs. suppressors inside the tumor may be important in determining the outcome of immune responses inside tumors. LIGHT interacts with its two receptors to stimulate different kinds of cells inside the tumor to establish a unique environment leading to augmentation of priming and recruitment of anti-tumor T cells. This may be a means of generating a dominantly pro-inflammatory environment, resulting in the rejection of both primary tumor and metastases. In addition, the LIGHT-mediated environment may possibly modulate immune suppressive mechanisms inside the tumor, which is an efficient means of converting the anti-inflammatory environment inside tumor to a pro-inflammatory one. This ideal environment would more rapidly expand the effector cells at the tumor site, while blocking local suppressive factors to form a positive loop to favor the anti-tumor immunity. Finally, it is likely that LIGHT-mediated tumor environment can work synergistically with current immunotherapeutic strategies, and other non-immune suppressive traditional therapies to achieve favorable clinical outcomes for cancer patients.

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Abbreviations

HVEM

herpesvirus entry mediator

LIGHT
: *lymphotoxin*-like, shows *i*nducible expression, and competes with herpes simplex virus *g*lycoprotein D for *h*erpesvirus entry mediator, a receptor expressed by *T* lymphocytes

LTβR
: lymphotoxin-β receptor

DC
: dendritic cells

DLN
: draining lymph nodes

TLS
: tertiary lymphoid structure

SLC
: secondary lymphoid tissue chemokine

Ad
: adenovirus

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Biography

Yang-Xin Fu is a Professor in Department of Pathology and Attending Physician at the University of Chicago. Dr. Fu received his MD in Shanghai Medical University and Ph.D from University of Miami and completed his pathology residency at Washington University, St. Louis. The basic research program in his laboratory is focused on understanding the biological consequences arising from signaling by the Lymphotoxin-β receptor and related molecules in the development and function of primary, secondary, and tertiary lymphoid tissues. His recent studies have defined the roles of these molecules in autoimmunity and inflammation and developed new strategies to target tumor cells.

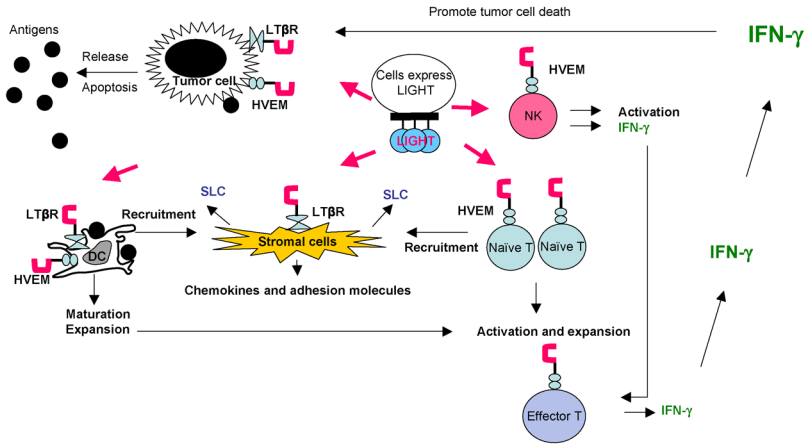

Figure 1. LIGHT enhances priming of anti-tumor T cells

Membrane-bound LIGHT stimulates stromal cells via LTβR to upregulate chemokines, such as SLC, and adhesion molecules to recruit naïve T cells and DCs into the tumor tissue. LIGHT promotes the survival, expansion and maturation of DCs, which possibly prime the T cells in situ. LIGHT also costimulates recruited naïve T cells, possibly through HVEM, in the present of tumor antigen for their activation and expansion. NK cells, which express HVEM, can be activated by LIGHT to produce IFN-γ to facilitate the expansion and differentiation of T cells and production of abundance of IFN-γ. Tumor cells signaled by LIGHT via LTβR and/or HVEM may become apoptotic in the presence of IFN-γ leading to antigen release and better priming of anti-tumor immunity.

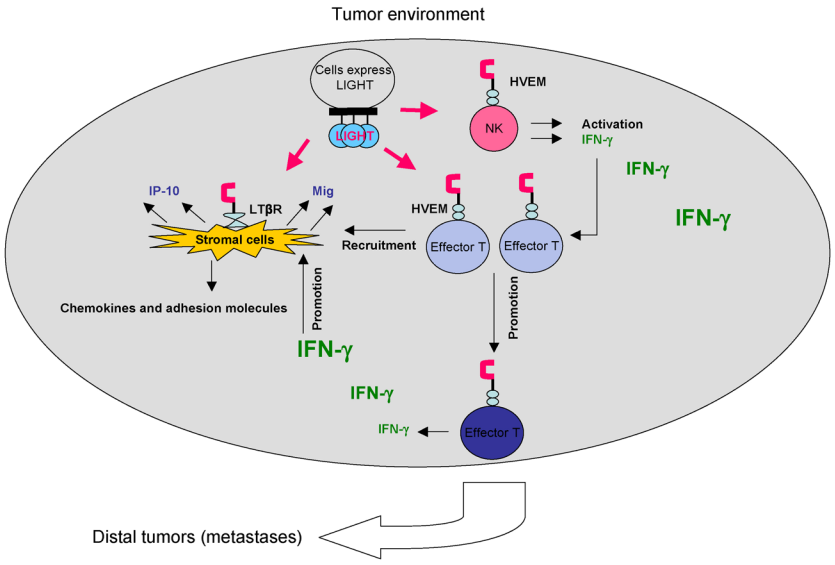

Figure 2. LIGHT recruits and promotes effector T cells inside the tumor tissue

Membrane-bound LIGHT stimulates stromal cells via LTβR to upregulate chemokines, such as IP-10 and Mig to recruit activated T cells into the tumor tissue. LIGHT may also stimulate the coming T cells for their further activation and expansion. NK cells activated by LIGHT through HVEM produce IFN-γ to facilitate the expansion, differentiation and production of more abundance of IFN-γ by T cells. IFN-γ in turn promotes the production of IP-10 and Mig to form a positive loop to recruit and promote effector T cells in the tumor tissue. The functional tumor antigen-specific T cells from LIGHT-mediated environment may traffic systemically for eradication of metastases.