CELL CYCLE
2016, VOL. 15, NO. 1, 25–40
http://dx.doi.org/10.1080/15384101.2015.1121324

REVIEW

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Inhibitory leukocyte immunoglobulin-like receptors: Immune checkpoint proteins and tumor sustaining factors

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ABSTRACT

Inhibitory leukocyte immunoglobulin-like receptors (LILRBs 1-5) transduce signals via intracellular immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that recruit protein tyrosine phosphatase non-receptor type 6 (PTPN6 or SHP-1), protein tyrosine phosphatase non-receptor type 11 (PTPN11 or SHP-2), or Src homology 2 domain-containing inositol phosphatase (SHIP), leading to negative regulation of immune cell activation. Certain of these receptors also play regulatory roles in neuronal activity and osteoclast development. The activation of LILRBs on immune cells by their ligands may contribute to immune evasion by tumors. Recent studies found that several members of LILRB family are expressed by tumor cells, notably hematopoietic cancer cells, and may directly regulate cancer development and relapse as well as the activity of cancer stem cells. LILRBs thus have dual concordant roles in tumor biology – as immune checkpoint molecules and as tumor-sustaining factors. Importantly, the study of knockout mice indicated that LILRBs do not affect hematopoiesis and normal development. Therefore LILRBs may represent ideal targets for tumor treatment. This review aims to summarize current knowledge on expression patterns, ligands, signaling, and functions of LILRB family members in the context of cancer development.

ARTICLE HISTORY
Received 23 September 2015
Accepted 12 November 2015

KEYWORDS
cancer; CD85; HLA; ILT; immunoglobulin-like transcript; immunoreceptor tyrosine-based activation motif; Immunoreceptor tyrosine-based inhibitory motifs; ITAM; ITIM; leukemia; leukocyte immunoglobulin-like receptor subfamily B; leukocyte immunoglobulin-like receptor; LILRB; LIR; MHC; phosphatase; SHIP; SHP-1; SHP-2; signal transduction

Introduction

Immunoreceptor tyrosine-based inhibitory motif (ITIM) was first described in 1995. This conserved motif consists of 6 amino acids (S/I/V/LxYxxI/V/L) located in the cytoplasmic portion of certain transmembrane receptors.[1] Proteome-wide analysis identified 109 human ITIM-containing receptors.[2] Conformational changes induced by ligand binding results in Src kinase-mediated phosphorylation of tyrosine in the ITIM, which in turn leads to the recruitment of SH2 domain-containing phosphatases. The ITIM-containing receptors bind tyrosine phosphatases SHP-1 or SHP-2 with the exception of immunoglobulin (Ig) G Fc receptor II-B (FcγRIIB), which only recruits the inositol-phosphatase SHIP.[3-5] The first amino acid of ITIM affects binding specificity; isoleucine at the first position (IxYxxL/V) favors SHP-1 binding, whereas leucine (LxYxxL/V) favors SHIP.[6] Phosphatase activation usually inhibits immune cell activation. Therefore these receptors are classified as immune inhibitory receptors. The downstream signaling of ITIM remains largely undefined, although known substrates of SHP-1 include the activated immunoreceptor tyrosine-based activation motif (ITAM), spleen tyrosine kinase (Syk), Src, zeta-chain associated protein kinase 70-kDa (ZAP70), Lck/Yes-related novel protein tyrosine kinase (Lyn), phosphatidylinositol-4-phosphate 3-kinase (PI3K), phospholipase C gamma (PLC-γ), and Vav 1 guanine nucleotide exchange factor (Vav1).[7-10]

In contrast to the immune inhibitory ITIM, the activated immunoreceptor tyrosine-based activation motif, abbreviated ITAM, results in immune activation. The ITAM has a conserved amino acid sequence of YxxL/Ix(6-8)YxxL/I and is located in the cytoplasmic tail of membrane proteins. ITAM transmits signals from various membrane receptors including B cell receptors, T cell receptors, activating leukocyte Ig-like receptors (LILRs), certain activating natural killer (NK) cell receptors, and Fc receptors to name a few.[11] Like ITIM-containing receptors, ligand binding of the ITAM-related receptor triggers Src kinase-mediated tyrosine phosphorylation within the ITAM, followed by recruitment and activation of tyrosine kinases (Syk in myeloid cells or ZAP-70 in lymphoid cells), usually resulting in immune activation.[11]

The leukocyte Ig-like receptor subfamily B (LILRB) is a group of type I transmembrane glycoproteins with extracellular Ig-like domains that bind ligands and intracellular ITIMs. This important group of ITIM-containing receptors contains 5 members, LILRB1 to LILRB5, also called CD85J, CD85D, CD85A, CD85K, and CD85C, respectively, or leukocyte Ig-like receptors (LIR1, LIR2, LIR3, LIR5, and LIR8, respectively). LILRBs 1–4 were also named Ig-like transcripts (ILT2, ILT4, ILT5, ILT3, respectively). Several LILRBs were cloned in 1997.[12-15] In 2001, the names LILRB and LILRA were officially given to the inhibitory receptors and the activating receptors, respectively.[16] These receptors are encoded in a region called

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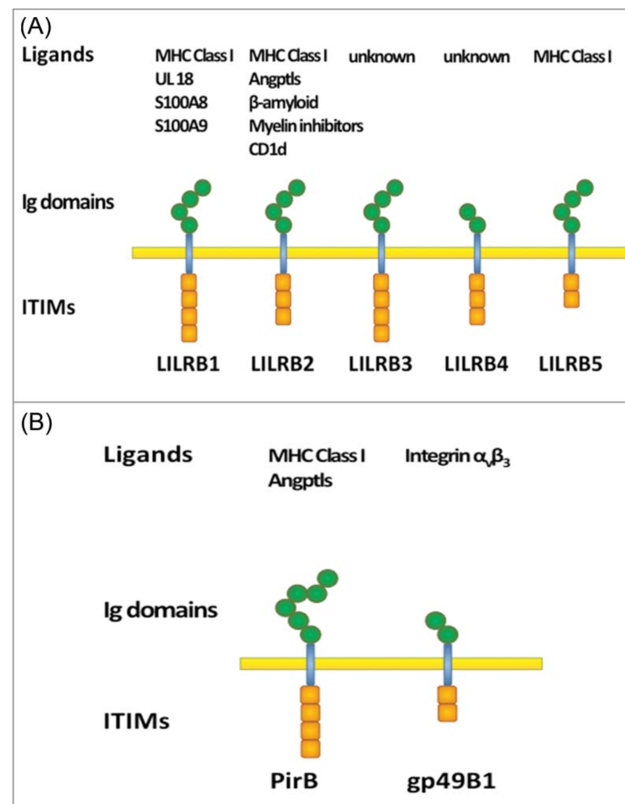

Figure 1. Domain structure of (A) human LILRBs and (B) mouse orthologs. Extracellular Ig-domains are depicted as hexagons and intracellular ITIMs are depicted as boxes.

leukocyte receptor complex at chromosomal region 19q13.4 in human.[12,17] The domain organizations of the LILRBs are depicted schematically in Figure 1A.

LILRBs are primate and human specific, with only 2 mouse orthologs, paired immunoglobulin-like receptor B (PirB) [18] and gp49B1,[19] known so far (Fig. 1B). Due to rapid evolution of LILRBs, animal models are of limited value, and the biological function and clinical significance of these receptors are not well understood. LILRBs were reported to be predominantly expressed in hematopoietic lineage cells and to suppress activation of various types of immune cells. LILRBs expressed on osteoclasts were reported to regulate osteoclastogenesis,[20] and LILRB2 on hematopoietic stem cells (HSCs) supports *ex vivo* expansion of HSCs.[21,22] LILRBs expressed on neurons regulate axon regeneration and have been implicated in neuropathology of Alzheimer's disease.[23,24] Because the immune-suppressive function of LILRBs is similar to that of immune checkpoint proteins such as CTLA4 and PD-1,[25] LILRBs are considered to be immune checkpoint factors.[26] Importantly, several groups including ours recently showed that LILRBs and a related ITIM-containing receptor LAIR1[27-30] are expressed on and have tumor-promoting functions in various hematopoietic and solid cancer cells.[21,31,32-46,47] Therefore, in addition to the role in immune checkpoints, which is indirectly tumor-supportive, LILRBs are also capable of directly sustaining cancer development. There are excellent recent reviews of structural, functional, and genetic features of LILRBs and related molecules and their functions in immune system-related diseases.[3,5,48-50] In this report, we aim to review the evidence that implicates LILRB family members in cancer development.

Ligands for ITIM-containing receptors

Known ligands for ITIM-containing receptors can be roughly divided into 3 groups: membrane-bound proteins (e.g., major histocompatibility complex (MHC) Class I or human leukocyte antigen (HLA) Class I molecules for LILRB1, 2, and 5),[51-53,54] extracellular matrix proteins (collagens for LAIR1),[27] and soluble proteins (e.g., antibodies for FcγRIIB).[55] Some of the ligands and signaling pathways for LILRBs have been identified,[12,21,23,24,52-54,56] but many uncertainties remain. LILRB1 and LILRB2 bind classical and non-classical MHC molecules.[12,51,52] Several non-MHC or non-HLA ligands also bind to LILRBs 1 and 2, including S100A8 and S100A9 for LILRB1,[57] and CD1d,[56] several angiopoietin-like proteins (Angptls),[21,22] oligomeric β-amyloid,[24] myelin inhibitors reticulon 4 (RTN4, Nogo66), myelin associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp) for LILRB2.[23] No ligands have been identified for LILRB3 or 4. Relatively little is known about LILRB5, but, recently, evidence that HLA-Class I heavy chains are LILRB5 ligands was reported.[54] The known ligands for PirB, the mouse ortholog of LILRB2/3, include MHC class I and Angptls.[20,21,58,59] gp49B1, the mouse ortholog of LILRB4, reportedly interacts with mouse integrin $\alpha v\beta 3$.[60] Human integrin $\alpha_v\beta_3$ does not bind to LILRB4, however. What is known about LILRBs ligands is summarized in Figure 1.

Relevance to cancer

The interactions between ligands and LILRBs are proposed to serve as immune checkpoints, although certain LILRBs act on a

broader array of immune cell types than the classical immune checkpoint proteins CTLA4 and PD-1.[26] Upon stimulation by ligands such as HLA-G on tumor cells, LILRBs inhibit immune activation thus indirectly supporting tumor development. What is surprising is that LILRBs and related receptors are expressed by tumor cells and appear to have direct tumor-sustaining activity. Multiple pieces of evidence suggest that LILRBs and related receptors directly support development of certain tumors. First, LILRBs are up-regulated or specifically expressed in some cancer cells. For example, LILRB4 is expressed at higher levels on primary human acute myeloid leukemia (AML) cells, especially M5 subtype AML cells, than on normal counterparts.[31,61] LILRBs, a related receptor LAIR1, and a number of ITIM-containing receptors are upregulated in Philadelphia chromosome positive acute lymphocytic leukemia (Ph^+ B-ALL) cells compared to normal pre-B cells.[46] LILRB4 is not expressed by normal B cells but is expressed in about 50% of B cell chronic lymphocytic leukemia (B-CLL) cells.[40] LILRBs are also specifically expressed or up-regulated on lung cancer, gastric cancer, breast cancer, and pancreas cancer cells.[32-34,38,41,42] Second, the expression of LILRBs correlates with survival of AML and Ph^+ B-ALL patients.[31,46] Third, silencing of LILRB2, 3, or 4 in human AML cell lines inhibits cell growth *in vitro*.[31] Finally, inhibition of expression of LAIR1 abolishes leukemia development in different xenograft models.[31,46] While LILRBs support tumor development, individual knockout of *PirB* or *gp49B1* (the known mouse orthologs of human LILRBs) or of *LAIR1* failed to induce overt defects in normal hematopoiesis.[21,62-65] Because LILRBs act as both immune checkpoint molecules and tumor sustaining factors and do not affect hematopoiesis and normal development, they have potential as targets for tumor treatment.

LILRB1

LILRB1 (also known as CD85J, ILT2, LIR1, and MIR7) has 4 ITIMs on the cytoplasmic side, and its extracellular portion has 4 immunoglobulin domains.[12,15] LILRB1 is the most widely distributed of the LILRBs with expression on certain NK cells, monocytes/macrophages, eosinophils and basophils, dendritic cells (DCs), subsets of T cells, B cells,[5,12,13,15] decidual macrophages,[66] progenitor mast cells (but not mature mast cells),[67] and osteoclasts.[20] LILRB1 is expressed uniformly on monocytes and B cells, but the expression of LILRB1 on NK cells varies between individuals due to a significant degree of diversity within the LILRB1 locus,[68] promoter choice, and translational repression.[69] Various ligands are known to interact with LILRB1, including HLA class I molecules (e.g., HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, and HLA-G) with affinities in μM range.[51,53,70,71] Of note, LILRB1 binds more strongly to HLA-G than to classical HLA class I molecules [53] and dimerized HLA-G induces more efficient LILRB1 signaling than the monomeric form.[72] LILRB1 also binds UL18, an HLA class I homologue that is encoded by human cytomegalovirus [12] with more than 1000-fold higher affinity than that for regular HLAs.[73] LILRB1 interacts with the α3 domain and β2-microglobulin of class I proteins and the analogous region of UL18 [53,73,74] but does not bind HLA-B27 lacking β2-microglobulin.[75] In addition, S100A8 and S100A9, 2 calcium-binding proteins, interact with LILRB1.[57]

Activation of LILRB1 transduces a negative signal that down-regulates the immune response and cytotoxicity, exerting inhibitory effects on NK cells, monocytes/macrophages, DCs, T cells, B cells, osteoblasts, and other cells. However, LILRB1 was also reported to be an activating receptor in NK cells, macrophages, DCs, T cells, and some cancer cells under certain contexts.

NK cells

LILRB1 expressed on NK cells can inhibit immune activity of these cells.[12,13,76-78] The binding of HLA-G to LILRB1 up-regulates LILRB1 expression in NK cells, antigen-presenting cells, and T cells,[79] and the ligand/LILRB1 interaction inhibits the polarization of NK-cell lytic granules by blocking accumulation of microtubule organizing center and F-actin at the area of contact, intracellular Ca^{2+} mobilization, and IFN-γ production.[80] HLA-G binding to LILRB1 on NK and macrophages also inhibits its cytotoxicity and inflammation toward trophoblasts, circumventing undesired anti-fetus immune responses during pregnancy.[81,82] LILRB1 also regulates roles of NK cells in cancer immunotherapy. With the progression of breast cancer, the expression of LILRB1 on NK cells increases with concomitant decrease in functions of NK cells.[83,84] Blockage of LILRB1 can restore the cytotoxicity function of NK cells in triple negative breast cancer.[84] LILRB1 may act cooperatively with other receptors, such as killer cell Ig-like receptor (KIR) in NK cell line NK92, to exert inhibitory effects.[85] Inhibition of both NKG2A and LILRB1 induce significant killing of AML and ALL cells by resting KIR-deficient NK cells, suggesting that NKG2A, LILRB1, and KIR might be promising NK cell targets for treatment of acute leukemias.[86] Interestingly, LILRB1 may also mediate activating signaling through its immunoreceptor tyrosine-based switch motif (ITSM).[87] NK cell-mediated inhibition of HIV-1 replication in monocyte-derived DCs is mediated by the interaction between LILRB1 on the NK cells with S100A9, a non-HLA class I calcium-binding protein, which is expressed on the DCs.[57,88]

Monocytes/macrophages

LILRB1 can inhibit monocyte activation signals. The binding of HLA-DR to LILRB1 inhibits Ca^{2+} mobilization in monocytes.[13] Co-ligation of LILRB1 with Fc receptor I (CD64) decreases tyrosine phosphorylation of the Fc receptor γ chain and Syk molecules and inhibits intracellular Ca^{2+} mobilization.[89] The expression of LILRB1 decreases in activated decidual macrophages and increases in activated decidual $CD4^+$ T cells, leading to the secretion of IL-4, a cytokine critical for successful pregnancy, from $CD4^+$ T cells.[90] Interestingly, upregulated HLA-G on human breast cancer cells may interact with LILRB1-expressing $CD68^+$ cells and $CD8^+$ cells to aid infiltration into breast cancer tissues, contributing to tumor development.[91] In contrast, HLA-G homodimer binds LILRB1 on $CD14^+$ macrophages and induces cytokine secretion [87]; in this scenario LILRB1 acts as an activating receptor.

DCs

The level of LILRB1 decreases following DC activation by CpG-DNA and inflammatory stimuli.[92] Both up-regulation [93] and down-regulation [94] of LILRB1 are observed during the differentiation from monocyte precursors to DCs. Continuous ligation of LILRB1 during DC differentiation confers a distinctive cell phenotype profile, decreases the susceptibility to CD95-mediated cell death, and inhibits cytokine secretion and the immunostimulatory function of DCs.[93] In immature human monocyte-derived DCs, crosslinking of LILRB1 inhibits osteoclast-associated receptor-mediated intracellular Ca^{2+} mobilization, cytokine production, T cell proliferation, and resistance to survival factor deprivation.[95] Trophoblast HLA-G may down-regulate allogeneic T cell proliferation by binding with antigen-presenting cells.[96] Urenda et al. observed that the levels of circulating plasmacytoid DCs (pDCs) are correlated with disease activity in systemic lupus erythematosus (SLE) patients and that the expression of LILRB1 is diminished in both pDCs and myeloid DCs (mDCs) from these patients, suggesting that lack of LILRB1 may underlie the defective immune-regulation in SLE patients.[97] HIV-1-infected elite controllers (who maintain undetectable HIV-1 replication in the absence of antiviral therapy) exhibit strong and selective upregulation of LILRB1 and LILRB3, which significantly increase the antigen-presentation abilities of circulating mDCs.[98] LILRB1 also mediates cytokine secretion by mDCs.[98] The complex effects of LILRB1 may be partially due to high levels of polymorphism and mutation of its gene.[98]

T cells

Although LILRB1 can only be detected on the surface of a subset of T cells,[12,13,99,100] it is expressed in the cytoplasm of all human T lymphocytes.[101] The expression of LILRB1 is increased on anti-viral CD8 T cells during chronic infection.[102] Soluble anti-LILRB1 stimulates, but crosslinked antibody inhibits, proliferation and functions of antigen-specific T cells.[102-104] LILBR1 plays a negative regulatory effect on the activation of T cells by inhibiting phosphorylation of linker for activation of T cells (LAT) and of ERK1/2.[105] LILRB1 competes with CD8 in binding to HLA class I molecules and modulates the activity of $CD8^+$ T cells.[53] The HLA-G/LILRB1 interaction on myeloid-derived suppressor cells (MDSCs) expands the population of MDSCs, which inhibited the proliferation and functions of T cells.[106] In a transgenic mouse model in which LILRB1 is expressed on T, B, NK, and natural killer T cells, the interaction of LILRB1 and H-2D^b, a murine MHC class I molecule, results in impaired development and function of T cells.[107] Tumor-cell-expressed HLA-G interacts with LILRB1 on Vγ9Vδ2 T cells or $CD8^+$ T cells to inhibit cytotoxicity of these T cells.[108] LILRB1 also mediates activation signaling. For example, interaction of cytomegalovirus protein UL18 and LILRB1 on $CD8^+$ T cells causes non-MHC-restricted lysis of virus-infected cells by resting and activated $CD8^+$ T cells [109] and IFN-γ production by T cells.[110]

B cells

Crosslinking of LILRB1 inhibits antigen-induced B cell activation and suppresses antibody production.[13,111] Interaction between HLA-G and LILRB1 inhibits B cell differentiation, chemotaxis, Ig secretion, and proliferation by G0/G1 arrest through dephosphorylation of AKT, GSK-3β, c-Raf, and Foxo proteins.[112] Apoptotic $LILRB1^+$ B cells may contribute to the overwhelming cytokine release and the impairment of the immune memory of malaria patients.[113]

Osteoclasts

LILRB1, like LILRBs 2-4, is expressed on immature osteoclasts. During osteoclastogenesis, LILRBs are tyrosine phosphorylated and constitutively associate with SHP-1. LILRB1, LILRB3, and LILRB4 inhibit differentiation of osteoclasts.[20]

Cancer development

As summarized above, tumor cell-expressed HLA-G can interact with LILRB1 on various types of immune cells possibly enabling immune evasion. LILRB1 is directly expressed on certain cancer cells, including AML cells (especially in monocytic AML cells),[31] neoplastic B cells (including B cell leukemia, B cell lymphoma, and multiple myeloma cells [35,36]), T cell leukemia and lymphoma cells,[37] and gastric cancer cells.[38] There is evidence that LILRB1 protects primary cutaneous $CD8^+$ and $CD56^+$ T cell lymphomas from cell death [37] and that its expression on human gastric cancer cells contributes to enhanced tumor growth.[38] In contrast, binding of soluble or nanoparticle-aggregated HLA-G with LILRB1 on neoplastic B cells inhibits cell proliferation.[35] In addition, blocking of LILRB1 on myeloma or lymphoblastic cells in culture using neutralizing antibodies did not affect cell lysis mediated by NK cells.[39] Context-dependent LILRB1 function in cancer biology warrants further investigation.

LILRB2

LILRB2 (also known as CD85D, ILT4, LIR2, and MIR10) contains 4 extracellular immunoglobulin domains, a transmembrane domain, and 3 cytoplasmic ITIMs. It is expressed on hematopoietic stem cells, monocytes, macrophages, dendritic cells, basophils in some individuals,[21,52,89] decidual macrophages,[66] mast cell progenitors,[67] endothelial cells,[114] and osteoclasts [20] but not on lymphoid cells. LILRB2 binds to multiple types of ligands, notably HLA class I molecules,[52] CD1d,[56] Angptls,[21,22] myelin inhibitors (including Nogo66, MAG, and OMgp [23]), and β-amyloid.[24] Unlike LILRB1, LILRB2 does not require β2-microglobulin in the complex to bind HLA ligands.[75] Cis interaction between LILRB2 and HLA ligands on the same cell has been reported.[115] We demonstrated that multimeric Angptls are superior to HLA-G in terms of binding and activating LILRB2.[22]

Studies on the function of LILRB2 have shown that this receptor plays a physiological role in several tissues. In hematopoietic lineages, LILRB2 has been associated with down modulation of immune response through various mechanisms. Crosslinking of LILRB2 with FcγR *in vitro* led to inhibition of FcR-mediated signaling in monocytes [89] and to serotonin release in a LILRB2-transfected basophilic cell line.[52] Up-regulation of LILRB2 induced dendritic cell tolerance.[116] Investigations into the role of LILRB2 in HIV have demonstrated that stronger binding between LILRB2 and HLA class I molecules is positively associated with viral replication, suggesting that this

interaction leads to a blunted immune response.[117] LILRB2 and LILRB4 are up-regulated in antigen presenting cells in response to *Salmonella* infection, suggesting a role of these receptors in balancing the inflammatory response in face of bacterial infection.[118] Our lab has shown that LILRB2 contributes to *ex vivo* expansion of HSCs likely through inhibition of differentiation.[21] LILRB2 is also expressed and activated on immature osteoclasts during osteoclastogenesis.[20] In neurologic tissues, LILRB2 suppresses axonal regeneration via binding to myelin inhibitors [23] and promotes the development of Alzheimer's disease through interaction with β-amyloid.[24]

LILRB2 plays various roles in cancer biology as well. Expression of LILRB2 has been reported in various cancer cells including AML, especially the monocytic subtype,[31] some chronic lymphoblastic leukemia (CLL),[40] primary ductal and lobular breast cancer,[41] and human non-small cell lung cancer.[42] [32-34] By contrast, LILRB2 is not expressed by normal lymphoid cells or normal breast tissues.[40] [41] PirB, the mouse ortholog of LILRB2 and LILRB3, is expressed on MLL-AF9 AML cells including AML stem cells.[21] The functional role of LILRB2 is still under investigation, but in lung cancer, LILRB2 supports cancer cell development and survival.[32]

LILRB3

LILRB3 (also called CD85A, ILT5, LIR3, HL9) contains 4 extracellular immunoglobulin domains, a transmembrane domain, and 4 cytoplasmic ITIMs. Expression of LILRB3 has been reported on monocytes, monocyte-derived osteoclasts, neutrophils, eosinophils, basophils, osteoclasts,[20] and progenitor mast cells.[67] There is significant polymorphism in the gene encoding LILRB3.[48]

The ligand for LILRB3 is unknown, and relatively little is known about the function of LILRB3. In human basophils, coligation of LILRB3 with FcεRI inhibits Fc receptor-mediated cell activities *in vitro*.[119] When LILRB3 is co-ligated with LILRA2 or IgE receptors on basophils, release of histamines, interleukin-4, and cysteinyl leukotrienes is inhibited.[5,48] LILRB3 is also proposed to be an inhibitor of allergic inflammation and a contributor to uncontrolled immune responses and autoimmunity.[48] Polymorphisms in *LILRB3* are linked to graft-versus-host disease in animal models and to the allergic response.[48] As do several other LILRBs, LILRB3 inhibits differentiation of osteoclasts.[20]

Certain myeloid leukemia, B lymphoid leukemia, and myeloma cells express LILRB3.[43] Of note, the observed co-expression of LILRB3 with stem cell marker CD34 and with myeloma marker CD138 suggests a role in cancer development.[43] Indeed, inhibition of LILRB3 expression in human leukemia cell lines blocks cell growth.[31] Antibodies against LILRB3 induce cytotoxicity of LILRB3-expressing cells via complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.[43] LILRB3 thus is a potential target for anti-cancer therapy.

LILRB4

LILRB4 (also known as CD85K, ILT3, LIR5, HM18) is unique among LILRB family members in that it contains only 2 extracellular immunoglobulin domains; it also has a transmembrane domain and 3 ITIMs. Expression of LILRB4 has been reported on dendritic cells, monocytes and macrophages,[12,14,120] [14,121] progenitor mast cells,[67] endothelial cells,[122] and osteoclasts.[20] Interestingly, the gene encoding LILRB4 is one of the most polymorphic of all receptor-encoding genes with at least 15 known single-nucleotide polymorphisms [123]; the significance of this polymorphism is unclear. LILRB4 is conformationally and electrostatically unsuitable for MHC binding,[124] and the ligand for human LILRB4 is unknown.

Monocytes

LILRB4 is expressed on monocytes and can be upregulated by IFNβ and vitamin D3 during central nervous system inflammation.[125] Upon crosslinking of LILRB4 to HLA-DR, SHP-1 is recruited to LILRB4 through the 2 ITIMs and inhibits tyrosine phosphorylation of downstream cellular signaling, which inhibits Ca^{2+} mobilization in monocytes.[14] Similarly, co-ligation of CD11b or FcγRIII with LILRB4 inhibits monocyte activation.[14] Crosslinking of FcγRI with LILRB4 also significantly reduces FcγRI-induced TNFα production and phosphorylation of Lck, Syk, LAT, ERK, and c-Cbl via recruitment of phosphatases other than SHP-1.[126]

T cells

Literature showed that LILRB4 from other cell types was capable of inhibiting activation of T cells, on which an unknown ligand for LILRB4 may be expressed. DCs that express high levels of LILRB4 and LILRB2 promote conversion of alloreactive $CD4^+CD45RO^+CD25^+$ T cells to regulatory T cells (Treg).[116] Both membrane-bound and soluble LILRB4 inhibit T cell proliferation and induce differentiation of $CD8^+$ T suppressor cells (Ts) *in vitro* [127] and *in vivo*.[44] Injection of soluble LILRB4 protects allogeneic human pancreatic islet transplantation [128] and prevents graft-vs.-host disease [129] via induction of Ts cells. Secretion of cytokines, such as IL-1α, IL-1β, IL-6, IFN-γ, and IL-17A, from DCs,[130] and the transcriptional factor BCL6 [131] are important for Ts induction by LILRB4. On the other hand, LILRB4 expression in Treg cells can be negatively regulated by casein kinase 2, and $LILRB4^+$ Treg cells show attenuated T cell receptor-mediated signaling.[132]

Cancer development

LILRB4 expressed on immune cells may facilitate tumor immune escape. In humanized mouse experiments, both membrane-bound and soluble LILRB4, mainly produced by tumor-associated macrophages, support cancer cell escape from immune suppression through induction of $CD8^+$ T suppressor cells.[44] LILRB4 inhibits T cell proliferation via induction of anergy of $CD4^+$ helper T cells and differentiation of T suppressor cells, suggesting that a ligand or counter-receptor for LILRB4 is expressed on T cells.[127] LILRB4 is also expressed on MDSCs in human lung cancer patients, and shorter survival of patients is associated with elevated MDSC numbers and higher LILRB4 expression.[133]

LILRB4 is also expressed on surfaces of several types of cancer cells. Dobrowolska et al. found that LILRB4 is expressed in all M4 and M5 monocytic AML cells and that it is co-expressed with leukemia stem cell markers CD34 and CD117 in 39% and 50% cases, respectively.[61] Although LILRB4 is not expressed by

normal B cells, it was detected in 23 out of 47 patients with chronic lymphoblastic leukemia (CLL) cells with more lymphoid tissue involvement; LILRB4 levels may thus be able to predict the prognosis of CLL.[40] In solid tumors, Zhang et al. found that LILRB4 is moderately expressed in some gastric cancer cells and tissues; together with LILRB1, it may inhibit NK cell-mediated cytotoxicity to gastric cancer cells.[38] More than 40% of patients with certain solid organ tumor such as colorectal carcinoma, pancreatic carcinoma, and melanoma have soluble LILRB4 that can inhibit T cell immunity *in vitro*.[44,45] The supportive role of LILRB4 in solid cancers was evidenced by restoration of T cell responses upon treatment with anti-LILRB4 or by depletion of LILRB4 in serum.[44] An animal model of spontaneous ovarian cancer also showed that increased LILRB4 expression is associated with tumor development and progression.[134]

LILRB5

Expression of LILRB5 (also known as CD85C and LIR8) has been reported in subpopulations of monocytes, NK cells, and mast cell granules.[12,67] A very recent study showed that LILRB5 specifically binds to HLA-B7 and HLA-B27 heavy chains.[54] Due to relative paucity of studies on LILRB5, the functional role of this receptor is not clear. One study suggested that LILRB5 present in the mononuclear phagocytic system of liver might play a role in clearance of creatine kinase.[135] Within human mast cells, LILRB5 is expressed in cytoplasmic granules that are released after crosslinking of high-affinity IgE receptors, which hints at a possible role in mast cell inflammatory response.[67] LILRB5 is unique among LILRBs in that it is the only LILRB that is not highly expressed by M5 AML cells, and its expression level does not correlate with the overall survival of AML patients based on analysis of TCGA database of AML patients (https://tcga-data.nci.nih.gov/tcga/).

PirB

PirB is the mouse ortholog of LILRB2/3; it contains 3 functional ITIMs. It is expressed on many hematopoietic cells, such as HSCs, DCs, macrophages, neutrophils and eosinophils, B cells, and osteoclasts. Its ligands include MHCI and Angptls,[20,21,58,59] and PirB can interact in *cis* with MHCI expressed on the same cell.[115] PirB regulates cell activity via direct recruitment of tyrosine phosphatases SHP-1 and SHP-2 for downstream signaling.[5,21,62,136] Along with the well-documented activity of PirB in regulation of hematopoietic cells, there are also studies that show that PirB influences neuron and osteoclast activities and leukemia development in AML.[5,20,21,47,62,64,136-145]

DCs

Within DCs, the roles of PirB have been relatively well studied with effects including regulating cytokine-mediated signaling, inducing peripheral tolerance within the graft-versus-host disease context, and facilitating DC maturation.[64,136,137] PirB suppresses type I interferon secretion in plasmacytoid DCs.[64] When PirB is ectopically expressed in DCs, there is a significant decrease in morbidity and mortality within an allograft graft-vs.-host disease model with the DCs exerting a suppressive function on alloreactive T cells.[137] In apparent contradiction, the knockout of *PirB* was found to impair the maturation of DCs with a hypothesized alteration of cell signaling involving granulocyte-macrophage colony stimulating factor.[138]

Macrophages

The roles of PirB on macrophages appear to be diverse and depend on organs. In the hematopoietic system, differentiation of macrophage precursors and MDSCs is regulated by PirB expression.[47] The deficiency of PirB in MDSCs biases differentiation toward M1 macrophages, which significantly stifles tumor growth and prevents metastasis in an LL2 tumor model.[47] PirB inhibits the activity of intestinal macrophages to prevent the progression of inflammatory diseases such as Crohn's disease and ulcerative colitis; the knockout of *PirB* leads to an increased susceptibility to induced colitis.[139] PirB is also a negative regulator in alveolar macrophages and suppresses IL-4 induction of pulmonary fibrosis.[140]

Other hematopoietic cells

PirB is highly expressed in eosinophils with an unexpected contribution to both inhibitory and activating pathways.[142] PirB reduces eotaxin-induced chemotaxis yet promotes chemotaxis response to chitin-induced inflammation.[142] Increased PirB expression results upon differentiation of myeloid lineage cells and B cells.[146] PirB is also expressed on mouse HSCs and binds with Angptls to support *ex vivo* expansion of adults HSCs.[21] PirB is generally not expressed on mature T cells, but its ectopic expression in peripheral T cells contributes to the suppression of type 1 helper T cell immune response. The exclusion of PirB from mature T cells might allow prompt immune responses.[141]

Osteoclasts

The deletion of *PirB* in prefusion osteoclasts led to an accelerated rate of osteoclast formation *in vitro*, and the study authors concluded that PirB negatively regulates osteoclast development.[20] However, PirB-deficient mice show no signs of osteoporosis in models, possibly resulting from involvements of other factors.[20]

Neurons

PirB regulates neural plasticity in the visual cortex. It appears to act as a negative regulator in the nervous system. It stabilizes neuronal networks by minimizing structural changes, which correlates with the slower learning rates with age.[143-145] Blocking activity of PirB in cortical pyramidal neurons led to enhanced ocular dominance plasticity.[143-145] The deletion of *PirB* in a mouse stroke model resulted in more rapid recovery.[143]

Cancer development

PirB supports the development of AML in mouse models by maintaining self-renewal and inhibiting differentiation of these cancer cells.[21] In addition, PirB on MDSCs cancer cells suppresses differentiation of myeloid-derived suppressor cell into M1 macrophages, which in turn inhibits regulatory T cell activities and tumor development.[47]

gp49B1

gp49B1, or mouse LILRB4, is expressed on macrophages, mast cells, neutrophils, NK cells, and T cells.[147-151] It contains 2 extracellular Ig-like domains and 2 cytoplasmic ITIMs. Integrin $\alpha_v\beta_3$ is the only known ligand of gp49B1.[60] The ITIMs of gp49B1 interact with SHIP, SHP-1, and SHP-2,[152-154] and recruitment of SHP-1 to gp49B1 leads to inhibition of mast cell activation.[154] Co-ligation of gp49B1 and FcγRI blocked IgE-mediated mast cell activation.[19] Interaction of gp49B1 with integrin $\alpha_v\beta_3$ also inhibits mast cell activation [60] and CD40-mediated antibody production by memory and marginal zone B cells.[155] The gp49b-deficient mice [63,156] exhibit no development abnormality but show hypersensitivity of mast cells to ovalbumin-challenged anaphylaxis,[156] a great elevation of SCF-induced mast cell activation,[157] and increased neutrophil-dependent vascular injury induced by LPS.[149] The activation of mast cells and neutrophil infiltration in gp49b-deficient mice parallel increases in secretion of cytokines, such as IL-1β, MIP-1α, and MIP-2, upon type-II collagen antibody and LPS treatment.[158] Moreover, the combination of ovalbumin challenge with LPS sensitization induces gp49B1 expression on DCs. gp49B1 deficiency induces significant T helper cell type 2 immune response and pulmonary inflammation,[159] resulting from elevated chemokine (C-C motif) receptor 7 (CCR7) on gp49B1-deficient DCs and increased secretion of CCL21 by lung lymphatic vessels.[160]

LILRB signaling in cancer cells

Signaling through LILRBs starts with phosphorylation of tyrosine in ITIMs by Src kinases and results in activation of ITIMs and recruitment of SH2 domain-containing phosphatases SHP-1/SHP-2 or inositol-phosphatase SHIP.[3-5] Studies on mouse ortholog PirB furthered our understanding of the interaction between ITIM phospho-tyrosines and phosphatases.[62,136] Nevertheless, the signaling cascades downstream of LILRBs are not well characterized. ITIM-containing receptors likely have diverging signaling branches instead of the linear signaling cascades seen in the Janus kinase and signal transducer and activator of transcription (JAK/STAT) pathway. This may partially result from the large number of substrates of ITIM-recruited phosphatases including ITAMs, Src, Syk, ZAP70, Lyn, PI3K, PLC-γ, and Vav1.[7-10] This list is far from complete, and additional substrates likely interact with ITIMs. In addition, as reported in a number of studies, phosphatase-independent activities of SHP-1 and SHP-2 may take part in certain contexts.[31,161,162] Therefore, interaction of LILRBs with diverse ligands in different cells may result in activation of distinct signaling pathways. Here we summarize recent progress on analysis of LILRB signaling in cancer cells.

Signaling pathways of LILRB2 and PirB in cancer cells

PirB is associated with SHP-1 and SHP-2. Defective PirB signaling diminishes phosphorylation of SHP-1 and SHP-2 in AML cells.[21] In human cord blood CD34$^+$ cells, binding of the ligand Angptl to LILRB2 induces phosphorylation of CAMKIV. Concordantly, p-CAMKIV levels are decreased in PirB-deficient AML cells.[21] The interaction between Angptl2 and LILRB2 also plays an important role in non-small cell lung cancer (NSCLC).[32-34] One study found that LILRB2 drives B7-H3 expression via PI3K/AKT/mTOR signaling and that LILRB2 and B7-H3 co-expression is correlated with poor prognosis in NSCLC.[34] In a different study, inhibition of LILRB2 drastically decreased proliferation, colony formation, and migration of NSCLC cells, whereas Angptl2 binding to LILRB2 supported lung cancer development via the SHP2/CAMKI/CREB axis.[32] These findings suggest LILRB2 signaling may become a therapeutic target for certain AML subtypes and lung cancer.

LAIR1 signaling in leukemia cells

LAIR1 is a type I transmembrane glycoprotein with identical domain organization to LILRBs: LAIR1 has one extracellular Ig-like domain and 2 intracellular ITIMs that can recruit SHP-1 and SHP-2 upon activation.[27-30] LAIR1 is expressed on various hematopoietic cell lineages including CD34$^+$ progenitor cells.[163] Of note, LAIR1 appears to be dispensable for normal hematopoiesis.[31,46,65] The function of LAIR1 in different leukemias has not been completely clarified. In CLL, downregulation of LAIR1 correlates with increased risk of disease.[164,165] Antibody engagement with LAIR1 blocks AKT and NF-κB activation in CLL cells, leading to decreased cell proliferation.[165] In AML cells lines, the engagement of LAIR1 inhibits proliferation of blasts, induces apoptosis, and prevents nuclear translocation of NF-κB.[165-167] Most recently, 2 independent studies using *in vitro* and xenograft experiments showed that LAIR1 deficiency retards development of AML and B-ALL.[31,46] These same studies indicated that lack of LAIR1 expression leads to remission of leukemia and significantly longer survival time in different leukemia mouse models including MLL-AF9 (AML),[21,168,169] AML1-ETO9a (AML),[170] BCR-ABL (B-ALL),[46] and N-Myc (B-ALL).[171] Importantly, LAIR1 deficiency blocks leukemia development in primary or serial transplantation, suggesting that LAIR1 is critical for maintenance of the activity of AML stem cells.[31]

Interestingly, we found out that SHP-1, but not SHP-2, mediates LAIR1 signaling in AML cells and prevents exhaustion of AML stem cells *in vitro* and *in vivo*. SHP-1 is a negative signaling molecule for normal myeloid differentiation. However, it acts as a phosphatase-independent adaptor to recruit CAMKI for activation of the downstream transcription factor CREB in MLL-AF9-transformed AML cells. The LAIR1/SHP-1/CAMKI/CREB axis thus represents an appealing target for AML treatment.[31]

In the case of Ph$^+$ B-ALL, as demonstrated by Müschen's group, LAIR1, along with some other ITIM-containing receptors, supports development of leukemic cells.[46] LAIR1 mediates dephosphorylation of Syk by SHP-1 and SHIP. Hyperactive Syk tyrosine kinase activity is necessary and sufficient to induce death of these B-ALL cells. This suggests that the basic mechanism of negative selection of overactivated B cells still remains functional in transformed B-ALL cells. Therefore, the use of a negative B cell selection strategy might become a new strategy in overcoming drug resistance in Ph$^+$ B-ALL.[46]

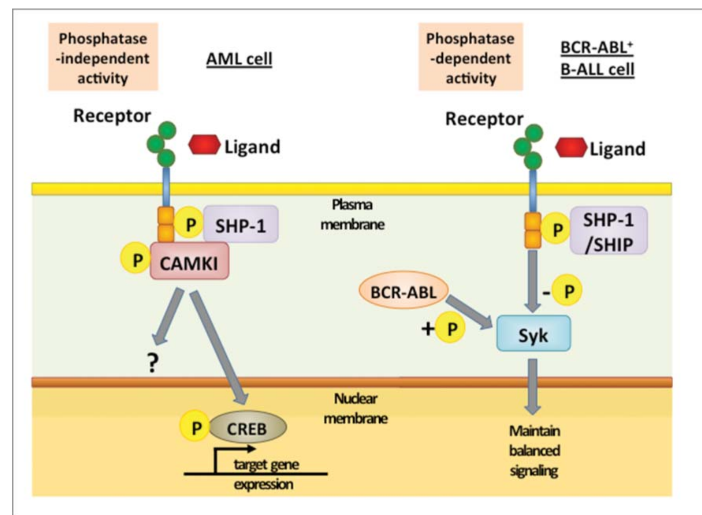

Figure 2. Downstream signaling of ITIM-containing receptor in different leukemia cells. In AML cells, binding of ligands or interaction between receptors activates LILRBs and results in tyrosine phosphorylation in ITIMs. This event is followed by recruitment of SHP-1, which acts as a phosphatase-independent scaffolding protein and forms a complex with the kinase CAMKI. CAMKI activation then induces phosphorylation and nuclear translocation of transcription factor CREB. In contrast, in BCR-ABL^{+} B-ALL cells, BCR-ABL-induced phosphorylation of Syk is balanced by SHP-1- and SHIP-mediated dephosphorylation. By preventing hyperphosphorylation of Syk, ITIM-containing receptors enable over-activated malignant B cells to avoid negative selection.

Perspectives and future work

LILRBs and related receptor LAIR1 support cancer cell survival and self-renewal in various types of cancer and represent attractive therapeutic targets. These ITIM-containing receptors support the development, drug resistance, relapse, or cancer stem cell activity of various types of cancer, although exact downstream signaling pathway may differ. It is noteworthy that independent studies demonstrated that SHP-1 was a key downstream regulator that is sufficient to promote the cancerous phenotype in AML and B-ALL. Therefore SHP-1 may act as a main signaling mediator downstream of ITIM-containing receptors and may exert its function via phosphatase-dependent or -independent mechanisms (Fig. 2). A number of questions regarding ITIM-containing receptors need to be answered before we can fully understand the biology of these receptors and apply this knowledge to cancer diagnosis and treatment.

Identification of ligands

Identification of ligands for LILRBs is a key step in understanding the biology of these receptors and how LILRBs function in tumor immune escape and cancer development and relapse. The ligands for LILRB3 and LILRB4 have not been identified yet. Given the fact that LILRB2 and LAIR1 each have multiple ligands, it will not be surprising if other ITIM-containing receptors have multiple binding partners. As the affinity of LILRB1 and LILRB2 for MHC-I is of low (μM) affinity, high-affinity ligands, co-ligands, or binding proteins of these 2 receptors may yet be identified. Several experimental techniques could be useful in identification of LILRB ligands such as expression cloning, crosslinking followed by co-immunoprecipitation and mass spectroscopy, protein arrays, and candidate screening. Newer techniques such as cell microarrays [172] and ligand-based receptor capture technologies [173] could also prove helpful in this effort.

Context dependent signaling

Why can inhibitory receptors support cancer cell activity? The tumor-supportive role of SHP-1 in certain acute leukemias may provide mechanistic insight into this question. A role for SHP-1 in AML development is supported by several lines of evidence: a) human LAIR1 is mainly associated with SHP-1 but not SHP-2 [174]; b) SHP-1 suppresses differentiation in some leukemia cells,[175] which is in line with the reported anti-differentiation activity of LAIR1 [176]; c) the deletion of SHP-1 was found to cause an increase in reactive oxidation species, inactivation of other phosphatases, and a drastic reduction in colony forming ability by upregulation of Arf and p53 [46]; and d) elevated SHP-1 expression has been reported to be correlated with the chronic phase of CML and with AML progression,[177] and SHP-1 inhibits apoptosis in freshly isolated leukemia cells.[178] SHP-1 is capable of binding to Grb2 in a phosphatase-independent manner [161]; however, the CAMKI recruitment of SHP-1 represents a different phosphatase-independent mechanism that appears to sustain AML stem cell activity,[31] and SHP-1 utilizes a phosphatase-dependent mechanism to support Ph^{+} B-ALL.[46] In contrast, SHP-1 is a negative regulator of growth of normal hematopoietic progenitors and overexpression of SHP-1 inhibits growth of cancer cell lines.[179-183] LAIR1 signaling negatively regulates myeloid leukemia and CLL.[165,166] Multiple studies have also reported decreased expression of SHP-1 in CML, AML, and pediatric acute lymphoblastic leukemia patients leading to the notion that loss of SHP-1 might be a critical step in development of leukemia [184,185] with poorer prognosis for patients.[177,186] It will be critical to determine the cell or tumor-stage specificity of the tumor-supportive and tumor-suppressive activities of SHP-1.

The possibility that SHP-1, SHP-2, and SHIP have overlapping but distinct roles in ITIM-containing receptor-mediated signaling in different cells is intriguing. It is generally agreed that SHP-2 plays a positive signaling role in the hematopoietic system, whereas SHP-1 is a negative

regulator of cell signaling. However, SHP-1, but not SHP-2, mediates LAIR1 signaling to support AML development.[31] SHP-2 is also known to act as an oncogene or as a tumor-suppressor depending on the type of cancers.[187] Whereas SHP-1 appears to be solely responsible for the tumor-promoting function of LAIR1 in AML cells,[31] both SHP-1 and SHIP support the development of Ph^{+} B-ALL.[46] It is reasonable to assume that the large number of substrates for these phosphatases and divergent downstream signaling contribute to the complexity. Identification of the cell and tumor contexts of SHP-1-, SHP-2-, and SHIP-mediated signaling and their respective substrates or interacting proteins and the full spectrum of LILRB downstream signaling in different cell types will be critical.

LILRBs and related ITIM-containing receptors in solid cancer

The tumor-supportive role of LILRBs extends beyond hematopoietic malignancies. Indeed, expression of LILRB1, 2, and 4 are reported in non-hematopoietic cancers such as gastric cancer, breast cancer, lung cancer, and pancreatic cancer.[32-34,38,41,42] Given the number of ITIM-containing receptors, each tumor type and subtype may express unique combinations. An improved understanding of ITIM-containing receptor biology will be critical as we seek to understand their individual and combined effects in these cancer cells.

Potential therapeutic approaches targeting LILRBs

The dual roles as immune checkpoint molecules and tumor-sustaining factors and a lack of apparent function in normal development and hematopoiesis suggest that LILRBs are ideal targets for treating cancer. Although LILRBs have been reported to regulate axon development [23] and osteoclast differentiation,[20] the potential side effects of LILRB inhibition may not be a big hurdle. For instance, a design of drug (such as antibody) that cannot cross blood-brain-barrier would spare the central neuronal system, and it has been shown that inhibition of LILRBs does not alter osteoclastogenesis *in vivo*.[20] Potential approaches to inhibition of LILRB signaling include targeting different segments of these signaling pathways. A possible approach would be to use recombinant soluble extracellular domains of these receptors or blocking antibodies to competitively block activity. Antibody conjugate therapeutics [188] that directly target LILRB-expressing malignant cells are also possible options. In addition, it will be interesting to test whether chimeric antigen receptors [189] engineered to target LILRBs and other ITIM-containing receptors are effective in treating hematopoietic malignancies. In parallel, inhibitors specific to phosphatase-dependent and/or independent SHP-1 activity have great potential. Finally, cloning of novel high-affinity ligands for LILRBs will provide novel insights into targeting signaling through these receptors.

Conclusion

The identification of LILRBs and their downstream signaling as potential therapeutic targets has reshaped our views regarding how cancer develops, how cancer cells differ from other cells, and how to treat this difficult disease. The studies reviewed here suggest that some leukemia cells have unique signaling pathways downstream of ITIM-containing receptors. These inhibitory receptors may enable the cancer cells to survive conventional therapies, resulting in tumor relapse. Because inhibition of the signaling of certain LILRBs directly blocks cancer growth and unleashes immune checkpoints that may suppress tumorigenesis, but does not disturb normal development, these receptors may represent ideal targets for treating cancer. The blockade of inhibitory receptor signaling in combination with conventional therapies may prove to be an effective strategy for elimination of leukemia cells as well as other types of cancer cells.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

We would like to thank the NIH (1R01CA172268), the Leukemia & Lymphoma Society (1024-14 and TRP-6024-14), the Robert A. Welch Foundation (I-1834), the Cancer Prevention and Research Institute of Texas (RP140402 and DP150056), and the March of Dimes Foundation (#1-FY14-201) for generous support.

Acknowledgments

We thank Drs. John E. Coligan, Eric O. Long, and Susan K. Pierce at NIAID for insightful discussions. We regret that we have been unable to cite many relevant primary references due to space limitations.

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