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Review Article

Leukocyte immunoglobulin-like receptor subfamily B: therapeutic targets in cancer

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ABSTRACT

Inhibitory leukocyte immunoglobulin-like receptors (LILRBs 1–5) transduce signals via intracellular immunoreceptor tyrosine-based inhibitory motifs that recruit phosphatases to negatively regulate immune activation. The activation of LILRB signaling in immune cells may contribute to immune evasion. In addition, the expression and signaling of LILRBs in cancer cells especially in certain hematologic malignant cells directly support cancer development. Certain LILRBs thus have dual roles in cancer biology—as immune checkpoint molecules and tumor-supporting factors. Here, we review the expression, ligands, signaling, and functions of LILRBs, as well as therapeutic development targeting them. LILRBs may represent attractive targets for cancer treatment, and antagonizing LILRB signaling may prove to be effective anti-cancer strategies.

Statement of Significance: Activation of LILRB signaling may contribute to immune evasion and support cancer development. The dual roles of certain LILRBs in cancer biology—as immune checkpoint molecules and as tumor-supporting factors—suggest that LILRBs may represent attractive targets for cancer treatment.

KEYWORDS: immunoreceptor tyrosine-based inhibitory motif; ITIM; immunoglobulin-like domain; immune inhibitory receptor; leukocyte immunoglobulin-like receptor subfamily B; LILRB; signal transduction; cancer

INTRODUCTION

Immunotherapy holds great promise for achieving long-lasting anti-cancer effects. In particular, immune checkpoint Programmed cell death protein 1 and ligand 1 (PD-1/PD-L1) blockade therapies have been successful for treating a small portion of cancers [1]. Developing approaches to identify more effective immune checkpoint targets is essential for successful application of immunotherapy to a broader range of cancers. Two features of PD-1 may hint us in these endeavors. First, activation of PD-1 as an immune inhibitory receptor involves the immunoreceptor tyrosine-based inhibitory motif (ITIM) and a related immunoreceptor tyrosine-based switch motif (ITSM) in its signaling domains [2]. ITIM consists of six amino acids (S/I/V/LxYxxI/V/L) [3], and ITSM is defined as TxYxx(V/I) [4]. The activation of ITIMs typically leads to the recruitment of tyrosine phosphatases SHP-1 and SHP-2 or the inositol phosphatase SHIP and the consequent inhibition of immune cell activation [5–7]. Therefore, ITIM-containing receptors represent a rich source of candidates for the next generation of immune checkpoint proteins. Second, PD-1 is expressed on exhausted T cells within the tumor microenvironment (TME). While ongoing efforts to scrutinize all inhibitory receptors on T cells are intensive, it is known that some other populations of

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immune cells, such as myeloid cells, are present in the TME in even larger numbers than T cells and can contribute to tumor immune evasion. For example, macrophages are the most abundant immune cell population in tumor tissues [8]. These immune cells possess the capacity to kill tumor cells and to prime or reactivate T cells. However, they become dysfunctional in the TME, turning into immunosuppressive cells that can support tumor development and suppress immune surveillance and attack. These immunosuppressive cells may include monocytic myeloid-derived suppressor cells (M-MDSCs), polymorphonuclear MDSCs, tumor-associated macrophages (TAMs), and immunosuppressive populations of dendritic cells (DCs), neutrophils, eosinophils, and B cells [9–14]. Immune inhibitory receptors on these cells may play key roles in their immunosuppressive functions. Reprogramming, removing, or blocking trafficking of these immunosuppressive cells is becoming an attractive anti-cancer therapeutic strategy [10]. To identify the next generation of immune checkpoint molecules, it is important to study the biology of ITIM-containing receptors that are expressed by immune cells in the TME.

There are more than 100 ITIM-containing receptors [15], including receptor families [3] such as leukocyte immunoglobulin-like receptor subfamily B (LILRB), certain killer cell immunoglobulin-like receptors (KIRs), and several sialic acid-binding immunoglobulin-like lectins (Siglecs). These receptors contain extracellular immunoglobulin (Ig)-like domains for ligand binding and intracellular ITIM domains to negatively regulate activation signaling in immune cells.

The LILRBs are a group of type I transmembrane glycoproteins with extracellular Ig-like domains that bind ligands and intracellular ITIMs that can recruit tyrosine phosphatases SHP-1, SHP-2, and the inositol phosphatase SHIP. The LILRB family contains five members LILRB1–LILRB5 (Fig. 1A), all of which were cloned in 1997 [16–19]. Historically, this family of receptors was also named as members of CD85, ILT, or LIR family (Table 1). In 2001, the name LILRB was officially assigned [20]. Because of their immunosuppressive functions, LILRBs are considered to be immune checkpoint factors [21] and may play significant roles in human immunity and cancer development.

LILRBs are primate-specific. The human LILRBs are encoded in a region called the leukocyte receptor complex (LRC) at chromosomal region 19q13.4 [16,20,22]. Like the inhibitory receptor PD-1 [23], the relatives of LILRBs exist in birds and mammals [24,25], although by phylogenetic definition these relatives are not considered LILRB homologs [26,27]. Paired immunoglobulin-like receptor B (PirB) [28] and gp49B1 [29] are the mouse relatives of LILRBs (Fig. 1B). Due to rapid evolution, the expression pattern and, in some cases, the ligands of these LILRB relatives are different from those of their human counterparts. Therefore, the PirB or gp49B1 knockout mouse models are of limited value for building and understanding of the biology of human LILRBs.

LILRBs are predominantly expressed by cells of the hematopoietic system. LILRBs may also be expressed by certain non-hematopoietic cells. For instance, LILRB2 is expressed on neurons, which has been implicated to regulate axon regeneration and is involved in the pathology of Alzheimer's disease [30,31]. LILRBs and a related ITIM-containing receptor LAIR1 [32–35] are abnormally expressed by certain cancer cells [36–53]. Overall, the immune cell-expressing LILRBs have immune inhibitory functions and thus are indirectly tumor-supportive, and the cancer cell-expressing LILRBs may directly regulate cancer development [54].

Similar to regulation of PD-L1 levels by external cues from TME, the expression of LILRBs can be regulated by both immunosuppressive and proinflammatory signals. The expression of LILRB1-4 can be upregulated by the immunoinhibitory cytokine IL-10 [55–57], and the LILRB4 level can also be elevated by the immunosuppressive hormone vitamin D3 [58,59]. On the other hand, LILRB2 and LILRB4 are also upregulated by the proinflammatory cytokines interferon (IFN)-α [60] and IFN-β [61], analogous to upregulation of PD-L1 by IFN-γ. Together, such induced increase of LILRB levels may enhance the immunosuppressive and tumor-promoting capacities of TME.

We hypothesize that the immunosuppressive myeloid cells is a key component of TME that inhibits tumor-specific immune responses and supports tumor development, and LILRBs are a major group of inhibitory receptors that regulate the immunosuppressive function of these tumor-supportive myeloid cells. Here, we review the signaling and functions of LILRBs in cancer development.

Leukocyte immunoglobulin-like receptor B 1 (LILRB1)

LILRB1, also known as CD85J, ILT2, LIR1, and MIR7, contains four extracellular immunoglobulin domains and four intracellular ITIMs [16,19]. LILRB1 is expressed on monocytes, macrophages, DCs, eosinophils and basophils, B cells, T cells, and natural killer (NK) cells, as well as on *in vitro* cultured cord blood-derived progenitor mast cells and osteoclasts [7,16,17,19,54,62–64]. It is the most broadly expressed member of the LILRB family.

Polymorphic expression of LILRB1

The expression of LILRB1 differs among cell types and individuals. LILRB1 is expressed uniformly on monocytes, macrophages, DCs, and B cells. In contrast, LILRB1 expression levels vary significantly on subsets of NK cells and T cells among individuals [54]. Moreover, LILRB1 can be upregulated on immune cells from individuals with cytomegalovirus (CMV) [65,66], renal transplant with CMV infection [67,68], rheumatoid arthritis [69], and late-stage solid tumors or hematologic malignancies [70–74]. Several mechanisms may explain the polymorphism of LILRB1 expression: (1) Myeloid cells and lymphoid cells use distinct promoters to drive the expression of LILRB1. Myeloid cells use the promoter proximal to the coding region, whereas lymphoid cells use the 5′ distal promoter with a sequence that represses protein translation [75,76]. A polymorphic enhancer that interacts with transcription

Table 1. Summary of ligands and expression of human LILRBs and mouse relatives, and clinical trials of antibodies targeting human LILRBs

Receptor	Alias	Ligands	Expression	Clinical trial
LILRB1	CD85J ILT2 LIR1 MIR7	MHC-I UL18 S100A8/9	NK cells Monocytes Macrophages Eosinophils Basophils DCs T cells B cells Mast cell progenitors Osteoclasts	
LILRB2	CD85D ILT4 LIR2 MIR10	MHC-I Angptls Nogo66 MAG OMgp β-amyloid SEMA4A CD1c/d CSPs	HSCs Monocytes Macrophages DCs Basophils Mast cell progenitors Endothelial cells Osteoclasts	MK-4830 (Merck) in phase 1/2 trial (NCT03564691) JTX-8064 (Jounce Therapeutics) in phase 1 trial (NCT04669899)
LILRB3	CD85A ILT5 LIR3 HL9		Monocytes Neutrophils Eosinophils Basophils Osteoclasts Mast cell progenitors	
LILRB4	CD85K ILT3 LIR5 HM18	ApoE CD166 CNTFR	Monocytes Macrophages DCs Mast cell progenitors Plasmablasts Treg cells Endothelial cells Osteoclasts	IO-202 (Immune-Onc Therapeutics) in phase 1 trial (NCT04372433) Merck announced phase 1 trial in solid tumors at an investor event, although no listing at clinicaltrials.gov is disclosed
LILRB5	CD85C LIR8	MHC-I	Monocytes NK cells T cells Osteoclasts Mast cell granules	
PirB		MHC-I Angptls Nogo66 MAG OMgp β-amyloid	HSCs DCs Macrophages Neutrophils Eosinophils B cells T cells Osteoclasts Neuronal cells	
gp49B1		Integrin $\alpha_V\beta_3$	Macrophages Mast cells DCs Neutrophils NK cells T cells Microglia Cardiomyocytes	

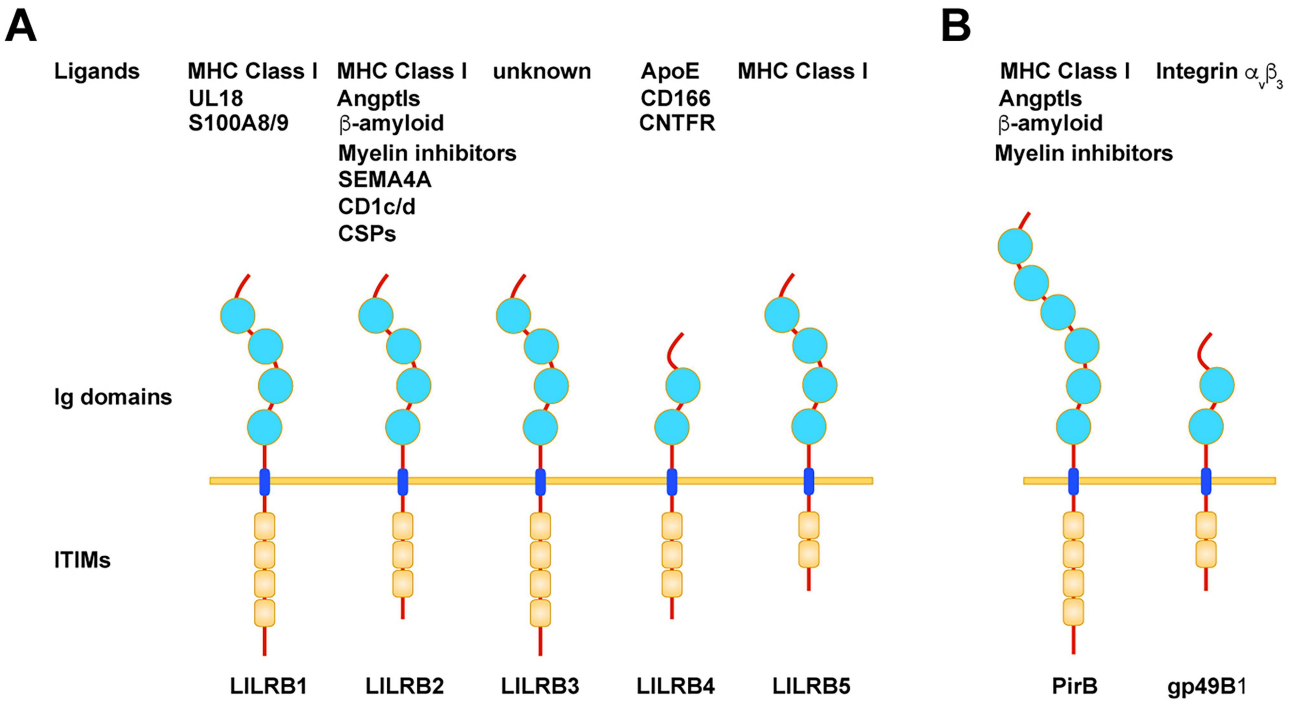

Figure 1. Domain structure of (A) human LILRBs and (B) mouse relatives. Extracellular Ig domains are depicted as circles and intracellular ITIMs are depicted as boxes.

factor Yin Yang 1 (YY1) [77], and several SNPs located in the regulatory region and coding region may play roles in the expression of LILRB1 on NK cells [76]. (2) Among NK cells, LILRB1 is mainly expressed on $CD56^{dim}$ NK cells [71,78], especially on terminally differentiated NK cells that express CD57 or multiple KIRs [79,80]. Adaptive NK cells, produced in response to viral infection, such as CMV or HIV infection, also highly express both CD57 and LILRB1 [81–83]. Similarly, LILRB1 is highly expressed on CD8 effector memory T cells that re-express CD45RA [65,69,75,84], a terminally differentiated effector T-cell subset that expresses CD57 [85]. The percentage of CD57 expressing T cells increases with age and CMV infection [65]. Differences in the abundance of these LILRB1 expressing NK and T-cell subsets among individuals may contribute to the differences in LILRB1 expression levels. (3) The expression of LILRB1 may be induced by extracellular stimuli. HLA-G is capable of upregulating LILRB1 expression on NK cells, T cells, and antigen-presenting cells [86]. Cancer cells [72] and M2 macrophages [87] also can upregulate the expression of LILRB1 on NK cells when co-cultured *in vitro*.

LILRB1 ligands

Multiple types of ligands have been identified to interact with LILRB1, including classical (HLA-A, HLA-B, and HLA-C) and non-classical (HLA-E, HLA-F, and HLA-G) major histocompatibility complex class I molecules (MHC-Is), UL18 (a CMV MHC-I homolog), calcium-binding proteins S100A8/9 and RIFIN proteins (parasite gene products that are expressed on the surface of infected erythrocytes) [16,88–96]. Antibody-opsonized dengue virus also can co-ligate LILRB1, which may contribute to the pathogenesis of dengue infections by inhibiting immune cell responses [97–99]. Thus, LILRB1 not only regulates the immune cell functions in response to MHC-I levels but may also be a target for immune evasion by viral and parasitic infections.

LILRB1 binds to MHC-Is with fast association and dissociation rates without a large reduction in conformational flexibility at the binding interface. This enables fast monitoring of the expression level of MHC-Is on target cells [100]. In competition against CD8, the first and second Ig-like domains of LILRB1 (D1-D2) interact with the $\alpha 3$ domain and $\beta 2$-microglobulin of MHC-Is and the analogous region of UL18 [88,90,101]. However, they do not bind $\beta 2$-microglobulin-free MHC-Is [102,103]. LILRB1 binds flexibly to the $\alpha 3$ domain and binds tightly to $\beta 2$-microglobulin [103]. The third and fourth Ig-like domains (D3–D4) may act as a scaffold [104].

LILRB1 signaling

Upon activation by its ligands, the ITIM tyrosine residues of the ITIMs of LILRB1 are phosphorylated and recruit the tyrosine phosphatase SHP-1. SHP-1 inhibits early signaling events triggered by activating receptors and subsequently suppresses the functions of immune cells, such as NK cells [16,17,86,105–111], monocytes, macrophages [17,112–114], DCs [114–119], T cells [16,17,90,120–129], and B cells [17,130,131], as reviewed previously [54]. For example, the co-ligation of LILRB1 and activating receptors such as TCR inhibits TCR signaling and actin cytoskeleton reorganization [126]. Lck, an Src tyrosine kinase, is required for ITIM phosphorylation and LILRB1

activation [126]. Notably, C-terminal Src kinase (Csk) may also be recruited by the phosphorylation of ITIM tyrosines of LILRB1 [132] (similar to LAIR1 [36]), which may inhibit the activity of Lck.

On the other hand, activating effects of LILRB1 were reported in some scenarios [54,93,133–136]. Although UL18 protein on target cells was able to inhibit the cytolysis function of NK cells [137], UL18 expressed on CMV-infected cells showed net activating effects on the IFN-γ production from NK and T cells [136]. The interaction of UL18 on CMV-infected cells with LILRB1 on CD8 T cells enhanced the cytotoxic activities of T cells in a non-MHC-restricted fashion [135]. Compared to LILRB1$^-$ NK cells, LILRB1$^+$ NK cells showed a greater potency in controlling of HIV-1 replication in monocyte-derived dendritic cells (MDDCs) *in vitro*, which is dependent on NK-DC contact but not on the cytotoxic activities of NK cells [133]. S100A9 expressed on HIV-1-infected MDDCs is a potential ligand for the activating function of LILRB1 on NK cells in controlling of HIV-1 replication [93]. Myeloid DCs from elite HIV-1 controllers, a small group of HIV-1-infected individuals being able to maintain undetectable HIV-1 viral loads without antiretroviral therapy, exhibit higher level of antigen-presenting activities and expression of LILRB1 and LILRB3 [134]. Inhibition of LILRB1 on MDDCs attenuated their activities in stimulating allogeneic T cells and secreting inflammatory cytokines [134]. LILRB1 expressed on certain types of hematologic malignant cells may also activate immune responses [42,138]. We will discuss this part in the next section. The mechanism underlying the activating effects of LILRB1 is unclear. It was suggested that the activating signaling of LILRB1 derives from a possible ITSM in its intracellular domain [139]. In certain cases, LILRB1 expressed on target cells can also induce an immune response [42,138].

LILRB1 in cancer

The cancer-related functions of LILRBs were noted on both LILRBs expressed on immune cells and on tumor cells *per se*. Accumulating evidence suggests that LILRB1 may be a molecular target for immunotherapy in patients with cancer. LILRB1 is upregulated on NK cells from certain cancer patients [70–74]. Furthermore, there is a strong association between the percentage of circulating LILRB1$^+$ CD8 T cells and the recurrence risk of non-muscle invasive bladder cancer [140]. Lastly, LILRB1 is also upregulated on the surface of TAMs [141].

LILRB1 blockade on immune cells can improve their functions against both solid tumors [73,84,141] and hematologic malignancies [71,74,142]. In particular, LILRB1 blockade enhances the immune responses of NK cells against solid tumor cells (breast cancers and melanomas) and cells of blood cancers such as acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM) *in vitro* [71,73,74,142]. Furthermore, LILRB1 blockade can synergistically promote the functions of immune cells in combination with other treatments *in vitro*. For example, LILRB1 blockade enhances tumoricidal activity of NK cells in combination with blockade of NKG2A and KIR [142], activation of NKG2D and CD16 [71,73], or lenalidomide, an immunomodulatory drug used for treating MM, MDS, and certain types of lymphoma. LILRB1 blockade can also improve cytolytic activity of effector CD8 T cells induced by bispecific T-cell engagers [84]. Notably, single-cell RNAseq data have shown that LILRB1 and PD1 receptors are expressed by distinct CD8$^+$ T-cell subsets in tumors. This result suggests that the combination of LILRB1 and PD-1 blockade may be required to fully promote the tumoricidal activity CD8$^+$ T cells [84]. Importantly, Chen *et al*. [71] reported that LILRB1 blockade by a specific antagonistic monoclonal antibody can improve the function of NK cells against leukemia and MM *in vivo* as assessed in xenograft murine models. Besides lymphocytes, LILRB1 blockade has been reported to enhance the anti-CD47-induced phagocytosis by macrophages against cancer cells [141].

In addition to immune cells, LILRB1 is also directly expressed on certain cancer and pre-cancer cells, such as AML cells (especially monocytic AML cells) [36,143], T-cell lymphoma cells [43], and neoplastic B cells, including B-cell leukemia, B-cell lymphoma, and monoclonal gammopathy of undetermined significance [41,42,138]. LILRB1 blockade can enhance immune cell responses against LILRB1-positive cancer cells [71,74,142]. By contrast, it was also reported that LILRB1 expression on certain types of hematologic malignant cells increased their susceptibility to immune cells. LILRB1 expression on transformed B lymphoid cancer cells improved the cytolytic function of Vδ2$^-$ $\gamma\delta$ T cells *in vitro*, by interacting with the MHC-Is on $\gamma\delta$ T cells [42,138]. Lozano *et al.* [138] reported that the expression of LILRB1 was lost on active MM cells, while remained at higher levels on asymptomatic MUGS and MM cells in complete remission (CR). Overexpression of LILRB1 on MM cell lines improved cytolytic functions of T cells and NK cells *in vitro*, by interacting with S100A9 [138]. These results suggest that LILRB1 on tumor cells stimulates immune responses in certain situations. More studies are needed to determine which cancer patients may benefit from LILRB1 blockade.

Leukocyte immunoglobulin-like receptor B 2 (LILRB2)

LILRB2, also known as CD85D, ILT4, LIR2, and MIR10, contains four extracellular immunoglobulin domains, a transmembrane domain, and three cytoplasmic ITIMs. It is expressed on hematopoietic stem cells, monocytes, macrophages, DCs, neutrophils [144,145], basophils [37,112,146], platelets [147], and activated CD4$^+$ T cells [148], as well as *in vitro* cultured endothelial cells [149], mast cell progenitors [63], and osteoclasts [64].

LILRB2 ligands

Known ligands of LILRB2 include classical (HLA-A, HLA-B, and HLA-C) and non-classical (HLA-E, HLA-F, and HLA-G) HLA class I molecules [16,104,146,150,151], class-I like proteins CD1c and CD1d [152,153], complement split products (including C3b, iC3b, C4b, and C4d)

[154], Angiopoietin-like proteins (Angptls) [37,155], myelin inhibitors (including Nogo66, MAG, and OMgp) [30], β-amyloid [31,156,157], and SEMA4A [148]. LILRB2 binds to HLA class I molecules with kinetics and affinities in the micromolar range. Unlike LILRB1, the binding of LILRB2 to HLA ligands does not require β2-microglobulin [102]. The D1 and D2 regions of LILRB2 are responsible for binding to HLA-I [102,104] and β-amyloid oligomers [156,157]. LILRB2 can bind to HLA ligands through *cis* interaction on the same cell [158] or *trans* interaction on a different cell. Multimeric Angptls may be superior to HLA-G in terms of binding and activating LILRB2 [155]. In contrast to the HLA-LILRB2 interaction [155], Angptls binding to the D1 and D4 regions of LILRB2.

LILRB2 physiological functions

LILRB2 plays physiological roles in multiple tissues. LILRB2 is involved in immunotolerance in pregnancy and transplantation [159]. HLA-G/LILRB2 interactions promote accumulation and the suppressive activity of MDSCs during human pregnancies [159]. LILRB1 and LILRB2 can also mediate graft tolerance by binding to HLA-G. Elevated HLA-G levels are positively correlated with better graft acceptance in patients with renal transplants [160]. Crosslinking of LILRB2 with FcγR *in vitro* led to inhibition of FcγR-mediated signaling in monocytes [112] and serotonin release in basophilic cells [146]. Upregulation of LILRB2 induced the tolerance of DCs [161]. Interaction of LILRB2 with HLA class I molecules is positively associated with viral replication in HIV, suggesting that this interaction leads to a blunted immune response [162]. HLA-F can bind to LILRB1 and LILRB2 expressed on antigen-presenting cells and influence susceptibility to and disease progression of endometriosis [163]. Upregulation of LILRB2 and LILRB4 in antigen-presenting cells in response to *Salmonella* infection suggests a role for these receptors in balancing the inflammatory response against bacterial infection [164]. Lu *et al.* demonstrated that LILRB2 is expressed on activated $CD4^+$ T cells, and the binding of SEMA4A to LILRB2 co-stimulates $CD4^+$ T cells and regulates Th2 differentiation [148]. LILRB2 is localized in neutrophil lipid rafts and rapidly moves to the cell surface upon neutrophil stimulation. This upregulated LILRB2 then enhances the inhibitory signals of HLA-G on the phagocytic function of neutrophils [144,165]. Our lab has shown that Angptl2 binding to LILRB2 on HSCs supports *ex vivo* expansion of HSCs, likely by inhibiting their differentiation [37]. LILRB2 and a mouse relative receptor PirB are expressed on human and mouse platelets, respectively. Angptl2, released from platelet α-granules, binds LILRB2 to inhibit agonist-induced platelet aggregation and spreading on fibrinogen [147]. During osteoclastogenesis, LILRB2 is expressed and activated on immature osteoclasts *in vitro* [64]. In neurologic tissues, LILRB2 inhibits axonal regeneration by interacting with myelin inhibitors [30] and accelerates the development of Alzheimer's disease via binding to β-amyloid [31].

LILRB2 in cancer

LILRB2 on immune cells regulates cancer development through interaction with its ligands. HLA class I molecules that are aberrantly expressed in a variety of human malignant cells interact with LILRB2 expressed on immune cells. This interaction is involved in tumor immune evasion. In non-small cell lung carcinoma (NSCLC) and colorectal cancer (CRC), the feedback loop for HLA-G/LILRB2 expression increases migration and metastasis of tumor cells [166,167]. In NSCLC cell lines, recombinant human HLA-G up-regulates LILRB2 expression in a dose-dependent manner and also activates ERK1/2 [166,167]. HLA-G/LILRB2 promotes CRC progression through AKT and ERK activation [166,167]. Of note, LILRB2 is also expressed on MDSCs and DCs in the TME of certain cancers. LILRB2 blockade reprograms TAMs into a proinflammatory phenotype, suppresses Treg infiltration, and promotes the efficacy of an immune checkpoint inhibitor [168]. Antibody blockade of LILRB2 inhibits receptor-mediated activation of SHP-1/SHP-2 and enhances proinflammatory responses. During macrophage maturation, LILRB2 antagonism inhibits AKT and STAT6 activation in response to the treatment of macrophage colony-stimulating factor (M-CSF) and IL-4 and enhances NFκB and STAT1 activation in response to LPS/IFN-γ stimuli. Transcriptome analysis revealed that LILRB2 antagonism alters genes involved in cell cytoskeleton remodeling, lipid/cholesterol metabolism, and endosomal sorting pathways and changes differentiation gene networks to polarize TAMs toward an inflammatory phenotype [168]. High expression of LILRB2 in DCs promotes DC tolerance, inhibits Th1 and CTL differentiation, and enhances the generation of type 2 cytokine-secreting Th2 and Tc2 cells [169,170]. LILRB2 on DCs diminishes the killing ability of CTLs by competitively binding to MHC-class I against CD8 or upregulating HLA-G in CTLs [171]. These findings suggest that LILRB2 is a promising myeloid immune checkpoint target.

LILRB2 is also expressed on various types of cancer cells, including AML (especially the monocytic subtype) [36,37], some cases of CLL [46], primary ductal and lobular breast cancer [47], NSCLC [38–40,48], esophageal cancer [172], CRC [166,173], endometrial cancer [174], and pancreatic cancer [175]. The expression of LILRB2 in AML cells [36,37] may directly regulate the cell fates of AML cells and also inhibit anti-cancer immunity (as LILRB4). In NSCLC, LILRB2 supports cancer cell development and survival [38]. LILRB2 is significantly higher expressed in earlier tumor stages (pT1-2) of both histological subtypes of squamous cell carcinoma and esophageal adenocarcinoma [172]. Angptl2/LILRB2 engagement has also been implicated in sustaining epithelial–mesenchymal transition during pancreatic ductal carcinogenesis [175]. However, much further investigation of LILRB2's roles in cancer is still needed.

Leukocyte immunoglobulin-like receptor B 3 (LILRB3)

LILRB3, also known as CD85A, ILT5, LIR3, HL9, contains four extracellular immunoglobulin domains, a

transmembrane domain, and four cytoplasmic ITIMs. It is restrictively expressed in myeloid cells, such as monocytes, granulocytes [176] (neutrophils, eosinophils [177], and basophils [178]), and DCs, as well as *in vitro* differentiated osteoclasts [64] and progenitor mast cells [63]. There is significant polymorphism in the gene encoding LILRB3 [179,180]. Polymorphism of LILRB3 led to development of LILRB3-specific antibodies in 5.4% of hematopoietic stem cell transplant patients who had different LILRB3 sequences from donors [17,49].

LILRB3 ligand

No ligand for LILRB3 has yet been identified. The commonly occurring LILRB3 allele binds to cytokeratin-8-associated ligand on necrotic glandular epithelial cells. This result suggests that cytokeratin-8-associated protein might act like damage-associated molecular patterns and be recognized by macrophages through LILRB3 [180].

LILRB3 physiological functions

LILRB3 may contribute to the negative regulation of immune responses. For example, crosslinking of LILRB3 suppresses FcαR-mediated neutrophil activation [12] and crosslinking of LILRB3 with LILRA2 or FcεRI in human basophils leads to inhibition of cell activation [178]. LILRB3 may also inhibit allergic inflammation and autoimmunity in Takayasu arteritis [181–184], and LILRB3 acts as an immunosuppressive regulator during sepsis [185]. The knockdown of LILRB3 in macrophages increases phagocytosis and antigen presentation [185], while blockage of LILRB3 facilitates proliferation and differentiation of T helper cells [185]. LILRB3, together with LILRB2, may mediate the inhibition of monocyte activation by glatiramer acetate [186].

LILRB3 in cancer

LILRB3 ligation on primary monocytes by antibodies led to inhibition of immune responses. Effects included polarization of immunosuppressive M2 macrophages, inhibition of T-cell proliferation, and suppressed allogeneic immune response in humanized mice that was engrafted with allogeneic human B-cell lymphoma cells [187]. In addition, the polymorphism of LILRB3 may influence the immune response to tumors [179,180]. LILRB3 is also expressed on certain myeloid leukemia, B lymphoid leukemia, and myeloma cells [49]. Inhibition of LILRB3 expression in human leukemia cell lines suppresses cell proliferation [36]. LILRB3 is co-expressed with stem cell marker CD34 and myeloma marker CD138. Specific allogeneic antibodies from hematopoietic stem cell transplant patients against LILRB3 may induce complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity of LILRB3-expressing cancer cells, which suggests that LILRB3 is a potential therapeutic target [49].

Leukocyte immunoglobulin-like receptor B 4 (LILRB4)

LILRB4 is also known as CD85K, ILT3, LIR5, and HM18. This receptor contains only two extracellular immunoglobulin domains, a transmembrane domain, and three ITIMs. The gene encoding LILRB4 is one of the most polymorphic receptors with at least 15 known single-nucleotide polymorphisms [188]. LILRB4 is expressed on monocytes and macrophages [16,18,189,190], DCs, plasmablasts [191], and Treg cells [192], as well as *in vitro* cultured progenitor mast cells [63], endothelial cells [193], and osteoclasts [64].

LILRB4 ligands

Unlike LILRB1/2, LILRB4 is conformationally and electrostatically unsuitable for MHC binding [194]. CD166 [195], ApoE [196], and CNTFR [197] were reported to bind LILRB4.

LILRB4 functions in monocytes

Expression of LILRB4 on monocytes can be upregulated by vitamin D3 [61]. Crosslinking of LILRB4 to HLA-DR, CD11b, or FcγRIII leads to recruitment of SHP-1 to LILRB4 and inhibits tyrosine phosphorylation of downstream cellular signaling, which in turn inhibits Ca^{2+} mobilization in monocytes [18]. Crosslinking of LILRB4 to FcγRI leads to recruitment of phosphatases other than SHP-1. This recruitment significantly reduces FcγRI-induced TNFα production and phosphorylation of Lck, Syk, LAT, ERK, and c-Cbl [198]. These effects are associated with suppression of FcγRI-dependent endocytosis and phagocytosis [199]. Overall, the inhibitory function of LILRB4 depends on its ITIMs [200]. In addition, LILRB4 is expressed on macrophages in atherosclerotic plaques of patients with coronary heart disease [201]. LILRB4 is also upregulated in the peripheral blood mononuclear cells of patients with pulmonary embolisms [202] or pulmonary tuberculosis [203]. Lastly, LILRB4 can be induced in tolerogenic MDDCs with a combination of TNFα and poly(I:C) [204].

LILRB4 functions related to T cells

LILRB4 expression in Treg cells can be negatively regulated by casein kinase 2, and $LILRB4^+$ Treg cells show attenuated T-cell receptor-mediated signaling [192]. On the other hand, LILRB4 from other cell types is capable of inhibiting activation of T cells. DCs that express high levels of LILRB4 and LILRB2 promote conversion of alloreactive $CD4^+CD45RO^+CD25^+$ T cells to Treg [161]. Increased expression of LILRB4 and LILRB2 on DCs in kidney transplant patients promotes allograft survival [205]. In addition, LILRB4 was reported to inhibit T-cell proliferation [206], protect allogeneic human pancreatic islet transplantation [207], and prevent graft-versus-host disease [208]. The inhibition of T cells by LILRB4 is regulated by secretion of cytokines, such as IL-1α, IL-1β, IL-6, IFN-γ, and IL-17A, from DCs [209], and the transcriptional factor

BCL6 [210]. Furthermore, LILRB4-expressing monocytic AML cells suppress T-cell proliferation and activation [196].

LILRB4 in cancer

LILRB4 is expressed on MDSCs [211], tolerogenic DCs [212], and TAMs [50] in the TME, which may contribute to tumor immune evasion. LILRB4 is expressed on both monocytic and polymorphonuclear MDSCs in human NSCLC patients. The shorter survival of patients is associated with a higher percentage of polymorphonuclear MDSCs with high LILRB4 expression [211]. Expression of LILRB4 is also inversely associated with survival of colon cancer patients and T-cell infiltration in the TME [213]. LILRB2 and LILRB4 are upregulated on tolerogenic DCs, and anti-LILRB4 antibodies reversed the T-cell inhibitory effect of these tolerogenic DCs [212]. LILRB4 was found to be expressed on $CD103^-$ colonic DCs that exhibit an enhanced ability to generate T regulatory cells [214]. LILRB4 is expressed on TAMs in human colon carcinoma, melanoma, and pancreatic cancer patients. LILRB4, mainly produced by TAMs, supports cancer cell escape from immune suppression in humanized mouse experiments [50].

LILRB4 is also expressed on the surface of several types of cancer cells. LILRB4 is expressed on monocytic AML cells and is co-expressed with leukemia stem cell markers CD34 and CD117 [215]. LILRB4 is also expressed on CMML and MDS cells [216]. However, it is not expressed on normal hematopoietic progenitor and stem cells [143,196,217]. Based on its unique expression and functions, LILRB4 is the best molecular target among LILRB members for treatment of monocytic AML. Antagonistic antibodies targeting LILRB4 [196,218], and antibody-derived biologics, such as anti-LILRB4 chimeric antigen receptor (CAR) T cells [217] and anti-LILRB4 antibody–drug conjugates (ADC) [219], may be attractive therapeutic candidates against AML and other hematologic malignancies. Although LILRB4 is not expressed by normal B cells, it was detected on plasmablasts and plasma cells from patients with systemic lupus erythematosus [60,191] and on antibody-secreting cells in patients with acute Kawasaki disease [220]. Importantly, LILRB4 is expressed on chronic lymphoblastic leukemia (CLL) cells with more lymphoid tissue involvement [46], MLL-rearranged B-ALL cells [221] and some MM cells [222]. In addition, LILRB4 is expressed at moderate levels in some gastric cancer cells and tissues. Together with LILRB1, it may inhibit NK cell-mediated cytotoxicity against gastric cancer cells [44]. Moreover, increased expression of a chicken receptor that is a relative of human LILRB4 on chicken spontaneous ovarian cancer cells is associated with tumor development and progression [223].

Signaling pathways of LILRB4 in cancer cells

Other than recruiting SHP-1 in normal monocytes, LILRB4 expressed on monocytic AML cells recruits SHP-2 upon activation by ApoE. LILRB4 further activates NFκB signaling and promotes its downstream gene expression, such as uPAR and Arginase-1, to inhibit T cells and support AML infiltration [196]. Interruption of the ApoE-LILRB4 interaction with LILRB4-blocking antibodies promotes T-cell activation and inhibits leukemia cell migration, suggesting therapeutic applications of anti-LILRB4 blocking antibodies in monocytic AML patients [218]. Furthermore, *in vitro* and *in vivo* evidence have shown that intracellular ITIMs of LILRB4 are critical for leukemia cell infiltration and T-cell suppression [224]. LILRB4 is subject to transcriptional regulation by Vitamin D [225] and IL-10 [55–57]. In addition, the expression of LILRB4 on monocytic AML cells is regulated by RNA m6A methylation [226]. Inhibition of RNA m6A demethylase sensitizes leukemia cells to T-cell cytotoxicity and overcomes hypomethylating agent-induced immune evasion [226]. In addition, monocytic AML, especially M5b AML expressing high level of LILRB4, is more resistant to the BCL-2 inhibitor [227]. Concordantly, genetic mutation of SHP-2, which mediates LILRB4 functions in monocytic AML, is highly associated with the resistance of leukemia cells to the BCL-2 inhibitor venetoclax [228]. In CLL cells, interferon gamma response and CTLA-4 signaling genes are positively correlated with LILRB4 expression [216]. Furthermore, in CLL cells, the expression of LILRB4 is driven by Deltex1 and LILRB4 inhibits AKT activation upon B-cell receptor stimulation [229]. Overall, LILRB4 signaling is context-dependent in different types of cancer cells and appears to be different from that in normal monocytic cells.

Leukocyte immunoglobulin-like receptor B 5 (LILRB5)

LILRB5, also known as CD85C and LIR8, contains four extracellular immunoglobulin domains, a transmembrane domain, and two ITIMs. The expression of LILRB5 has been reported in subpopulations of monocytes, NK cells, and T cells, as well as *in vitro* cultured osteoclasts and mast cell granules [16,63,230–232]. A recent study showed that LILRB5 specifically binds to HLA-B7 and HLA-B27 heavy chains [230]. Due to a relative paucity of studies on LILRB5, the functional role of this receptor is not clear. Several genome-wide association studies have highlighted LILRB5 variants whose expression is correlated with serum creatine kinase and lactate dehydrogenase levels. This correlation suggests an as yet unknown role for LILRB5 in muscle repair [233–235]. Mycobacteria exposure has been shown to upregulate LILRB5 expression in APCs derived from BCG vaccinated donors, indicating a possible role for LILRB5 in bacterial infection [231]. Within mature cord blood-derived mast cells, LILRB5 is expressed in cytoplasmic granules that are released after crosslinking of high-affinity IgE receptors. This hints at a possible role in mast cell inflammatory response [63]. 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 the analysis of TCGA data for AML patients (https://tcga-data.nci.nih.gov/tcga/).

Paired immunoglobulin-like receptor B (PirB)

There are two mouse genes encoding proteins resembling LILRBs in human, PirB and gp49B1. Due to the expression patterns and, in some cases, the ligands they recognize, there is no clear 1:1 counterpart relationship between human LILRBs to mouse PirB and gp49B1. PirB, considered the mouse relative of LILRB2/3, contains six extracellular immunoglobulin domains, a transmembrane domain, and four ITIMs. It is expressed on HSCs [34], DCs [236–238], macrophages [239], neutrophils [240], eosinophils [241], B cells [240], T cells [242,243], osteoclasts [54], and neuronal cells [30].

PirB ligands

PirB ligands include MHC-I [233], Angptls [37,64,244,245], β-amyloid [31], and myelin inhibitory molecules (MAG, Nogo, and OMgp) [30]. PirB can interact in *cis* with MHC-I expressed on the same cell [158]. The extended conformation of extracellular domains of PirB enables *trans*-cellular interaction with ligands, such as MAG and MHC-I [246].

PirB in the hematopoietic system

PirB is expressed on mouse HSCs and multiple hematopoietic lineages [37]. On DCs, PirB regulates cytokine-mediated signaling [236–238], inhibits type I interferon secretion [237], induces peripheral tolerance within an allograft graft-versus-host disease model by suppression of alloreactive T cells [238], facilitates maturation of DCs with a hypothesized alteration of cell signaling involving granulocyte-macrophage colony-stimulating factor [247], and produces IL-27 to suppress $CD4^+$ T cells [248]. PirB is also a negative regulator of intestinal macrophages to prevent the progression of inflammatory diseases such as Crohn's disease and ulcerative colitis [239]. PirB inhibits alveolar macrophages and suppresses IL-4 induction of pulmonary fibrosis [249]. Moreover, the high expression of PirB in eosinophils contributes to both inhibitory and activating pathways [241], such as inhibition of IL-13-mediated eosinophil activation [250]. Differentiation of myeloid lineage cells and B cells leads to upregulation of PirB [240]. Ectopic expression of PirB in peripheral T cells contributes to the suppression of type 1 helper T-cell immune response [251]. Expression of PirB on T cells may be associated with chronic autoimmunity [242,243].

PirB in the nervous system

PirB is expressed in cortical and hippocampal neurons and regulates visual cortical plasticity [252–254]. Interaction of PirB on neurons with β-amyloid oligomer leads to recruitment of cofilin to facilitate actin depolymerization and results in synaptic loss and cognitive deficits [31]. Interaction of PirB with myelin inhibitor molecules suppresses axonal outgrowth and regeneration via activation of SHP-1/SHP-2 signaling [255], PI3K/Akt/mTOR signaling [256], and Trk signaling pathways [257]. In addition, the binding of PirB to MHC-I molecules contributes to suppression of synaptogenesis [258,259].

PirB in cancer

PirB is upregulated on DCs during cancer progression; knockdown of PirB on DCs increases Th17 response and decreases Treg differentiation to suppress tumor growth in a mouse lung cancer model [260]. PirB highly expressed on DCs competes with CD8 for MHC-I binding and inhibits tumor antigen-specific $CD8^+$ T-cell proliferation and cytotoxic activity to support tumor immune escape in a syngeneic mouse lymphoma model [261]. The upregulation of PirB on tumor-infiltrating DCs can be inhibited by PD-L1 blockade [262]. It was also reported that Angptl2 binds to PirB and activates Notch signaling for activation and maturation of DCs and subsequent $CD8^+$ T-cell cross-priming in mouse melanoma and kidney cancer models [263]. PirB expressed on MDSCs suppresses differentiation of MDSCs into M1 macrophages, which in turn inhibits regulatory T-cell activities and tumor development [53]. Interaction of glatiramer acetate with PirB on MDSCs suppresses T cell by promoting IL-10 and TGFβ release [186]. On the other hand, PirB is expressed on mouse AML cells and supports AML development by maintaining self-renewal and inhibiting differentiation of leukemia stem cells [37]. Defective PirB signaling diminishes phosphorylation of SHP-1 and SHP-2 in AML cells [37]. By recruiting SHP-1/SHP-2, PirB further activates CAMKs and the downstream CREB signaling pathway to support leukemia progression [264].

Glycoprotein 49B1(gp49B1)

gp49B1 is a mouse protein resembling human LILRB4. It contains two extracellular Ig-like domains. Unlike human LILRB4, it contains two cytoplasmic ITIMs instead of three. It is expressed on macrophages, mast cells, DCs, neutrophils, NK cells, T cells, microglia, and cardiomyocytes [265–272].

gp49B1 ligand and functions

Unlike mouse PirB and human LILRB4, gp49B1 cannot be activated by ApoE [196]. Integrin $\alpha_v\beta_3$ is the only known ligand of gp49B1, and the integrin $\alpha_v\beta_3$/gp49B1 interaction inhibits mast cell activation [273]. Co-ligation of gp49B1 and FcγRI also blocks IgE-mediated mast cell activation [29]. The gp49B1-mediated inhibition of mast cell activation requires recruitment of SHP-1 by ITIMs [274], which may also interact with SHIP and SHP-2 [274–276]. Although gp49B1-deficient mice [277,278] exhibit no developmental abnormalities, mast cells in these mice exhibit hypersensitivity to ovalbumin-challenged anaphylaxis [277], elevated SCF-induced mast cell activation [279], and increased neutrophil-dependent vascular injury induced by LPS [267,280]. In addition, gp49B1 deficiency induces significant T helper cell type 2 immune responses and pulmonary inflammation [281]. These result from elevated expression of chemokine (C-C motif) receptor 7 (CCR7) on DCs and increased secretion of CCL21 by lung lymphatic vessels [282]. The decrease of gp49B1 on tolerogenic uterine DCs or decidual macrophages contributes to abnormal pregnancy outcomes by changing M1/M2 functional molecular expression,

synthesis of arginine metabolic enzymes, and cytokine secretions [264,283]. Moreover, gp49B1 is upregulated on macrophages in atherosclerotic lesions from mouse aortic roots. Deficiency of gp49B1 significantly accelerates the development of atherosclerotic lesions and increased the instability of plaques [201]. Deficiency of gp49B1 in bone marrow-derived macrophages in the lung exacerbates acute lung injuries via promotion of NFκB signaling [284]. Downregulation of gp49B1 with other Treg-related genes, including Ikzf2, Ikzf4, Tigit, and Il10, is found in atherosclerosis-driven Treg plasticity [285]. Furthermore, deficiency of gp49B1 promotes cardiac hypertrophy via elevated NFκB signaling and TGFβ expression in cardiomyocytes [272]. On the other hand, overexpression of gp49B1 in cardiomyocytes inhibits angiotensin II-induced cardiomyocyte hypertrophy via interaction between gp49B1 and SHP-2 and inhibition of NFκB signaling [286]. gp49B1 also recruits SHP-1, which inhibits TRAF6 ubiquitination and subsequently inactivates NFκB signaling and MAPK cascades in nonalcoholic fatty liver disease [287]. Finally, gp49B1 expression levels are elevated in activated microglia in transgenic APP/PS1 Alzheimer's disease mice [288] and aged mice [271].

In addition to infection, gp49B1 is also expressed on activated CD4 and CD8 effector T cells after allogeneic tumor challenge [269]. NK and T cells from gp49B1-deficient mice exhibit enhanced cell cytotoxicity activities, which suggests that gp49B1 is an inhibitory checkpoint on anti-tumor immune cells in TME [269]. Moreover, gp49B1 is increased on activated plasmacytoid DCs after toll-like receptor activation, which is correlated to the reduction of T-cell activity against leukemia cells [289]. In summary, gp49B1 may play important roles in various inflammatory diseases and cancer.

PERSPECTIVES AND FUTURE WORK

LILRBs inhibit anti-tumor immune activities and support cancer cell survival, self-renewal, and migration in various types of cancer, thus representing attractive therapeutic targets. Several key questions need to be addressed in order to better apply our knowledge to cancer diagnosis and treatment.

Identification of ligands

Identification of ligands for LILRBs is a key step to understanding the biology and function of these receptors in tumor immune evasion and cancer development. The study of chicken relatives of LILRBs suggested that the ancient ligands for these Ig-containing receptors were MHC class I and β2-microglobulin [24,25]. However, human LILRBs interact with both HLA and non-HLA ligands. Given the fact that LILRB1 and LILRB2 each have multiple ligands, it will not be surprising if individual LILRBs have multiple binding partners. High-affinity ligands, co-ligands, or binding proteins of LILRB1, 2, and 4 may have yet to be identified. The ligand for LILRB3 is still unknown. HLA-B27, a ligand of LILRB5, needs further functional validation. Several experimental techniques could be useful in identification of LILRB ligands such as expression cloning, crosslinking followed by co-immunoprecipitation and mass spectroscopy, protein liquid chromatography fractionation followed by reporter assays and mass spectrometry [196], protein arrays, candidate screening, cell microarrays [290] and ligand-based receptor capture technologies [291]. The identification of multiple Ig-containing receptors that interact with LILRBs [197] has new implications of signaling and functions of LILRBs. If these ligand/receptor interactions happen *trans* among different cells, our understanding of how LILRBs act may significantly change.

Context-dependent signaling and functions

The signaling and functions of individual LILRBs may share common features and also differ depending on their expression in normal immune cells, immune cells in diseased individuals (such as MDSCs, TAMs, and other immunosuppressive cells), hematological malignant cells, and solid cancer cells. A major question in the study of LILRBs and other classical ITIM-containing receptors is whether these inhibitory receptors have independent signaling or whether their signaling needs to be associated with those of activating receptors. It was proposed that the activity of the ITIM-containing inhibitory receptors requires ITAM-containing receptors [3,126]. In this model, an ITIM-containing receptor cannot activate by itself but needs to interact with an activating receptor. When the ITAM-containing activating receptor is activated, its ITAM recruits the Src tyrosine kinase [126], which phosphorylates and thus activates the ITIMs of the nearby inhibitory receptors. The recruitment of SHP-1 may subsequently dephosphorylate the ITAM and/or associated proteins, thus preventing further activation of the activating receptors [126]. This model explains TCR-, BCR-, and FcR-coupled LILRB signaling in T and B cells. Nevertheless, in monocytic cells, LILRB4 clustering *per se* without crosslinking with an ITAM receptor can induce SHP-1 recruitment [18]. In fact, the Src kinase Lck can activate the ITIM- and ITSM-containing receptor in the absence of ITAM receptors in an *in vitro* reconstitution system [292]. Further investigations are warranted to determine LILRB signaling and functions in malignant cells, in which ITIM-containing receptors may have acquired certain independent cancer-promoting activities due to an altered signaling context [36,196].

The cell-context-dependent difference of LILRB signaling and functions may result from a number of factors: (1) different extrinsic cues. The diversity of ligands of each receptor contributes to distinct function of each receptor in different microenvironments. In addition, different ligand binding at different epitopes of LILRBs can lead to different conformational changes of the receptors and consequently different signaling. (2) The interaction between LILRBs and other receptors. Most recently, it was demonstrated that multiple Ig-domain receptors interact with various LILRBs [197]. Such *cis* or *trans* interactions may regulate the signaling and functions of LILRBs differently in different cells. In addition, extracellular factors that bind to other receptors on the same immune cells could affect the feedback signaling of LILRBs [5]. (3) Different signaling

domains of different LILRBs. Due to variable sequences and context, not all ITIMs are equivalent. For example, it was suggested that a certain ITIM in LILRB1 was possibly an ITSM [139]. Although all LILRBs contain ITIMs, we found that certain ITIMs in different LILRB members were not interchangeable [224]. (4) Different levels of signaling molecules in different types of cells. The large number of substrates for SHP-1, SHP-2, and SHIP and divergent downstream signaling may contribute to the complexity. (5) Different transcriptional (such as LILRBs regulation by IL-10 [55–57] and LILRB4 by vitamin D3 [58,59]), perhaps translational, or post-transcriptional regulation of individual LILRBs may lead to formation of different interactomes.

The studies of LILRB biology in cancer cells may shed new lights on better understanding of the functions of LILRBs in immune cells in TME, and vice versa. For example, monocytic AML cells and immunosuppressive monocytic cells (including M-MDSCs and TAMs with monocytic origin) in cancer patients may share several characteristics: (1) both are monocytic cells marked by LILRB4 expression [50,196,211,217], (2) STAT3/NFκB/Arginase-1 axis is functionally active in both populations [293,294], and (3) both have robust migration abilities [10]. It is therefore possible that LILRB4 signaling in monocytic AML cells and M-MDSCs is similar, and antagonizing LILRB4 signaling by blocking antibodies may have anti-tumor effects in different applications such as treatment of leukemia (by directly targeting LILRB4 in leukemia cells) and treatment of certain solid cancers (by targeting or reprogramming LILRB4 in TME).

Overall, efforts to identify new ligands and study signaling and downstream effectors could lead to further determination of exact functions of LILRBs (antigen presentation, priming, activation, trafficking, reprogramming, and functions on cancer cells) in immune checkpoint biology.

Potential therapeutic approaches targeting LILRBs

Elucidation of underlying mechanism of LILRBs paves the way for the development of therapeutics for human malignances. LILRB1 expressed by macrophages mediate the secondary anti-phagocytic 'don't eat me' signals independently but cooperatively with the CD47-SIRPα pathway [141]. Anti-CD47 and anti-MHC class I or anti-LILRB1 might act in synergy to induce phagocytosis or immune system activation of macrophages. LILRB2 expressed by MDSCs or TAM suppresses anti-tumor immune activities in TME. Anti-LILRB2 monotherapy or combination with an anti-PD-1 antibody is in phase 1/2 clinical trial by Merck (MK-4830; Clinical Trial ID: NCT03564691; Table 1). Preliminary clinical data have shown that MK-4830 was well tolerated, and anti-cancer responses were observed in 10 patients treated with the anti-LILRB2 antibody MK-4830 in combination with pembrolizumab, 5 of whom progressed on prior anti-PD-1 therapies [295]. These data suggest that LILRB2 from immunosuppressive myeloid cells may contribute to drug resistance in the anti-PD-1 therapy. Other anti-LILRB2 therapeutics are also under preclinical development by Immune-Onc Therapeutics (IO-108) and in phase 1 clinical trial by Jounce Therapeutics (JTX-8064; Clinical Trial ID: NCT04669899; Table 1), respectively, to reprogram immune suppressive myeloid cells in solid cancers. Among all LILRB members, LILRB4 is clearly the best target for treating monocytic AML. It may also be a target for treating some other hematologic malignancies and solid cancers. By blocking ApoE-induced LILRB4 activation, an anti-LILRB4 antibody developed by Immune-Onc Therapeutics is in a phase 1 clinical trial as monotherapy for AML and CMML patients (IO-202; Clinical Trial ID: NCT04372433). An anti-LILRB4 antibody (h52B8) by Merck inhibits the immunosuppressive activities of monocytic MDSCs *in vitro* [296], and a phase 1 clinical trial for cancer treatment was announced (Table 1). In addition, based on the information that LILRB4 is specifically expressed by monocyte lineage but not hematopoietic progenitor and stem cells, the CAR-engineered T (CAR-T) cell and ADC therapeutics that directly target LILRB4-expressing monocytic AML cells have been generated [217,219]. Preclinical studies have shown that both LILRB4-targeting CAR-T and ADC have anti-leukemia efficacy but do not affect the stem cell activities and differentiation of hematopoietic progenitor and stem cells. Other potential approaches to inhibition of LILRB signaling include targeting different segments of their downstream signaling pathways, although the signaling of ITIM-containing receptors is considered to be divergent. In addition to cancer, these drugs may also benefit patients affected by other diseases including infectious diseases, autoimmune diseases, and neurodegenerative diseases.

CONCLUSION

The identification of LILRBs and their downstream signaling as potential therapeutic targets has reshaped our views of how cancer cells interact with the TME and the immune system, how cancer cells differ from other cells, and how to treat cancer. Numerous studies indicate that LILRBs and their signaling in infiltrating immune cells protect tumor cells from immune surveillance and attack. In addition, LILRB signaling in cancer cells, particularly in some leukemia cells, directly support cancer development in cell autonomous and immune-related manners. Since inhibition of the signaling of specific LILRBs unleashes immune checkpoints and directly blocks cancer growth with only mild toxicities, these receptors represent promising therapeutic targets for cancer treatment.

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CONFLICT OF INTEREST STATEMENT

M.D., H.C., X.L., J.X., S.J., N.Z., Z.A., and C.C.Z had several patent applications licensed to Immune-Onc Therapeutics. C.C.Z is a Scientific Advisory Board member with Immune-Onc Therapeutics. M.D. and Z.A. hold the positions of Assistant Editor and Deputy Editor-in-Chief, respectively, for Antibody Therapeutics and are blinded from reviewing or making decisions for the manuscript.

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