Review Article
LILRB4, from the immune system to the disease target

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Abstract: Leukocyte immunoglobulin (Ig)-like receptor B4 (LILRB4) is a member of leukocyte Ig-like receptors (LILRs), which associate with membrane adaptors to signal through multiple cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs). Under physiological conditions, LILRB4 plays a very important role in the function of the immune system through its expression on various immune cells, such as T cells and plasma cells. Under pathological conditions, LILRB4 affects the processes of various diseases, such as the transformation and infiltration of tumors and leukemias, through various signaling pathways. Differential expression of LILRB4 is present in a variety of immune system diseases, such as Kawasaki disease, systemic lupus erythematosus (SLE), and sepsis. Recent studies have shown that LILRB4 also plays a role in mental illness. The important role of LILRB4 in the immune system and its differential expression in a variety of diseases make LILRB4 a potential prophylactic and therapeutic target for a variety of diseases.

Keywords: LILRB4, immunology, tumor, leukemia, inflammation

Introduction

Leukocyte immunoglobulin-like receptor (LIL-RB4) is a kind of inhibitory receptor that plays a key role in immune checkpoint pathways. Inhibitory receptors also participate in achieving balance between activating and inhibitory actions to ensure immune responses to pathogens in the immune system. However, they not only protect the host from autoimmune responses, but also preserve peripheral tolerance [1]. LILRB4 also regulates immune responses, and its role in regulating immune responses is mostly controlled by its ligands [2].

The leukocyte Ig-like receptor (LILR) family, the members of which are also called leukocyte immunoglobulin-like receptors (LIRs or ILTs), has 13 members (two pseudogenes are included) [3, 4]. LILRs are one of the seven types of leukocyte immunoglobulin-like inhibitory receptors, along with killer cell immunoglobulin-like receptors 2D, killer cell immunoglobulin-like receptors 3D, glycoprotein receptors (such as GP-49), paired immunoglobulin-like receptors, leukocyte-associated Ig-like receptors and inhibitory IgG Fc receptors (such as FcγRIIb1), and they have been identified in the human hematopoietic system [5].

Structure

LILRB4 is an LILR and is encoded in the leukocyte receptor cluster, which is on human chromosome *19q13.4* [4-6]. The structure and function of LILRs are similar to those of other leukocyte receptor cluster receptors, such as killer cell immunoglobulin-like receptors [3].

There are many kinds of classifications of LILRs. Among all these classifications, the most classical one is the one proposed by Willcox. In this classification, LILRs are divided into two groups according to whether they have high conservation of major histocompatibility complex (MHC) binding residues to interact with MHC class I or MHC class I-like proteins [3]. Other classifications divide LILRs into two groups according the different motifs: the inhibitory LILR subfamily B group (LILRB1-5), which associate with mem-
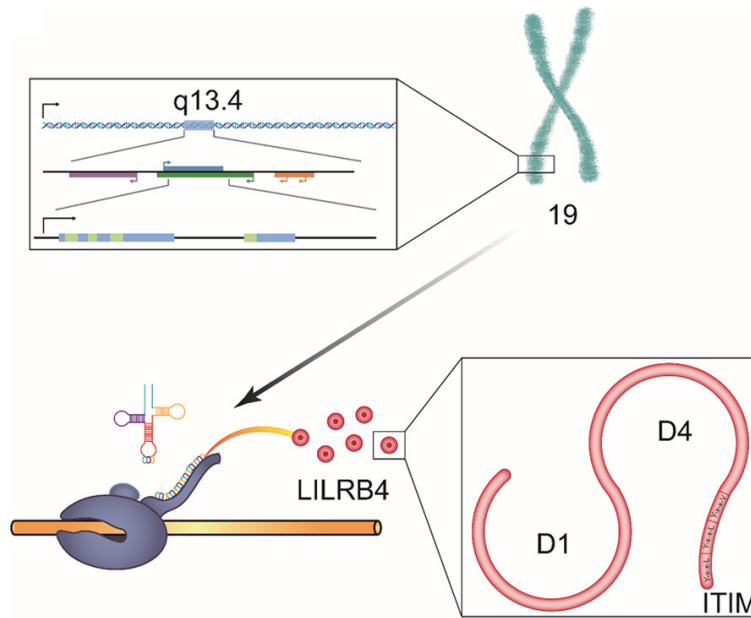
Figure 1. The structure of LILRB4. LILRB4 is encoded on human chromosome 19q13.4. It has two C-type Ig-like domains, D1 and D4. Three ITIMs of LILRB4 are of the YxxV sequence, and two are of the YxxL sequence, and they are located in the cytoplasmic tail. In addition, LILRB4 can recruit SHP-1 to downregulate activation signals, which is mediated by nonreceptor tyrosine kinase cascades.

Distribution

The expression of LILRB4 is confined to professional and nonprofessional antigen-presenting cells (APCs) [4]. LILRs are mainly expressed on cells of the myelomonocytic lineage [15], for example, monocytes, macrophages and dendritic cells [16]. In cells of the myelomonocytic lineage, LILRB4 is mostly expressed on APCs [17]. For many cells, such as APCs, myeloid-derived suppressor cells, plasmacytoid dendritic cells (DCs) and monocytic DCs, LILRB4 is generally referred to as a tolerogenic receptor [18]. In addition, by inhibiting the expression of costimulatory molecules, LILRB4-expressing APCs play key roles in controlling inflammation. Likewise, LILRB4 neutralization can increase antigen presentation [17]. Furthermore, LILRB4 can be expressed both on the cell membrane and/or in the cytoplasm [19].

Relationship with disease

As immune checkpoints are of great significance in autoimmune diseases, LILRB4 is a target for treating autoimmune diseases [20]. LILRB4 is associated with many kinds of immune diseases, such as Kawasaki disease and systemic lupus erythematosus (SLE). In addition, LILRB4 plays an effective role in inflammatory diseases. As nuclear factor-kappa B (NF-kappa B) is a common transcription factor that participates in angiogenesis, cell proliferation and cell survival [21], LILRB4 can promote cardiac dysfunction and fibrosis, and it can also lead to apoptosis via NF-kappa B signaling [22] and inflammation by activating NF-kappa B signaling through reduced phosphatase (SHP) 1 phosphorylation [23]. LILRB4 also has the ability to inhibit the development of tumors [24]. For example, LILRB4 is also an effective target for acute myeloid leukemia (AML) treatment [25]. Furthermore, it is presumed that LILRB4 also participates in the basic mechanisms of central nervous system (CNS) immune surveillance. As a result, LILRB4

brane adaptors to signal through multiple cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs), and the activating LILR subfamily A group (LILRA1-6), which associate with membrane adaptors to signal through immunoreceptor tyrosine-based activating motifs [7, 8]. In regard to signals transmitted by LILRs, both ITIMs and immunoreceptor tyrosine-based activating motifs are of great significance [9]. In addition, LILRB4 has three ITIMs [10] (**Figure 1**) [3, 5, 10]. Differences between LILRs are summarized in **Table 1** [3, 7, 11].

It is worth mentioning that most family members contain four C-type Ig-like domains in their extracellular region (designated D1, D2, D3, and D4); however, LILRB4 and LILRA5 have only two. In addition, LILRB4 is distinguished by an unusual domain organization, which consists of a classical LILR D1 domain and an immunoglobulin domain that is most similar to the membrane-proximal D4 domain of other LILRs [3, 12] (**Table 1**). In addition, LILRB4 has three specific amino acid residues, R56, R101, and V104 [13]. The natural ligand (s) for LILRB4 are still not clear [10]. However, the natural ligand for gp49B the mouse counterpart of LILRB4, is integrin avb3 [14].

Table 1. LILRs (omit the two pseudo-genes LILRP1 (ILT9) and LILRP2 (ILT11))

Receptor	Lg-like domains	Ligands	Expression	Diseases concerned	References
LILRA1 (LIR-6, CD85i)	D1, D2, D3, and D4	MHC-I, HLA-B27 FHC	monocytes and B cells	NA	[3, 7, 11]
LILRA2 (ILT1, LIR-7, CD85h)	D1, D2, D3, and D4	MHC-I	minor subsets of T- and natural killer (NK) cells, monocytes, macrophages, dendritic cells (DCs) and granulocytes	leprosy	[3, 7, 11]
LILRA3 (ILT6, LIR-4, CD85e)	D1, D2, D3, and D4	MHC-I	secreted by monocytes, B cells and subsets of T-cells	multiple sclerosis, Sjögren's syndrome, SLE, prostate cancer	[3, 7, 11]
LILRA4 (ILT7, CD85g)	D1, D2, D3, and D4	Ag 2 (BST2)	plasmacytoid DCs	NA	[3, 7, 11]
LILRA5 (ILT11, LIR-9, CD85f)	D1, D2	NA	monocytes and neutrophils	NA	[3, 7, 11]
LILRA6 (ILT8, CD85b)	D1, D2, D3, and D4	NA	monocytes	NA	[3, 7, 11]
LILRB1 (ILT2, LIR-1, CD85j)	D1, D2, D3, and D4	MHC-I	T, B, NK and myeloid cells	human cytomegalovirus (HCMV), dengue virus	[3, 7, 11]
LILRB2 (ILT4, LIR-2, CD85d)	D1, D2, D3, and D4	MHC-I	myeloid cells, hematopoietic stem cells	Alzheimer's disease	[3, 7, 11]
LILRB3 (ILT5, LIR-3, CD85a)	D1, D2, D3, and D4	NA	monocytes, DCs and granulocytes	Leukemia	[3, 7, 11]
LILRB4 (ILT3, LIR-5, CD85k)	D1, D4	unknown	monocytes, macrophages, DCs and plasma cells	SLE, Kawasaki disease, T. gondii, multiple sclerosis	[3, 7, 11, 17, 26]
LILRB5 (LIR-8, CD85c)	D1, D2, D3, and D4	HLA-B27 FHC	NK cells, monocytes and mast cell granules	NA	[3, 7, 11]

LILR: leukocyte immunoglobulin-like receptor; ILT: Leukocyte immunoglobulin-like receptor; MHC: major histocompatibility complex; SLE: systemic lupus erythematosus; HLA: human lymphocyte antigen; Ag: antigen; BST: bone marrow stromal antigen.

is associated with some neurological diseases, such as multiple sclerosis [26].

Physiological role of LILRB4

As one of the LILR family members, LILRB4's main function is to play a role in the immune response to infection [15]. It can participate in different mechanisms in many immune cells.

Immune cells

T cells

LILRB1 is the only human LILRB protein that can be expressed on T cells. LILRB1 expression on T cells can decrease the expression of chemokine receptors [27]. Although LILRB4 is not expressed on T cells, it can recognize unidentified ligands expressed on them [18], and it elicits T cell anergy or activation of regulatory T (Treg) cells or T suppressor cells [28]. Because of the bidirectional signaling properties of LILRB4, LILRB4 can not only transduce signals through its intracellular domain but also directly modulate the binding of its extracellular Ig-like domain [29]. As a result, LILR-Fcs, the soluble forms of LILR, are effective inhibitors of T cell proliferation, even in the absence of APCs [26]. LILRB4 can still inhibit T cells with its extracellular domain even when the ITIM-containing cytoplasmic tail is deleted. A study used a soluble form of LILRB4, expressed as an LILRB4-Fc fusion protein, and found that LILRB4-Fc could inhibit T cell immune/inflammatory responses as a result of inhibiting the release of inflammatory microRNA [30, 31]. For T cells with cognate specificity, LILRB4 can also induce anergy and plays a regulatory function [32].

In addition, T cells elicit the upregulation of LILRB2 and LILRB4 expression on APCs, which makes them tolerogenic to T cells. Furthermore, recombinant LILRB4-Fc has also been shown to activate T cell responses through induction of T helper cell (Th) anergy and differentiation of CD8+ T suppressor cells, as well as promotion of the induction of immunological tolerance [3, 12]. Blockade of inhibitory receptors leads to the generation of cytolytic CD8+ T cells that are able to recognize APCs and is of great significance when tumors and viruses invade bodies [33].

In Tregcells, the regulation of LILRB4 expression by CK2 is supposed to represent a regulatory mechanism of the adaptive immune response that enables the transient inhibition of suppressor cells at the time when a fulminant immune response is required [34]. In addition, Treg cells can produce interleukin-10 (IL-10), resulting in modulation of the dendritic cell phenotype via downregulation of MHC class II molecules, CD80 and CD86 and upregulation of LILRB4 [35].

Granulocytes

Granulocytes, including neutrophils, basophils, and eosinophils, provide a rapid response in the early stages of immune challenge through the release of secretory granules. LILRB1, LILRB2, LILRB3, and LILRA2 are expressed by eosinophils [9].

Human neutrophils can act as nonprofessional APCs. In adaptive immunity, human neutrophils play an immunoregulatory role. On circulating human neutrophils, some coinhibitory molecules, such as LILRB2 and LILRB3, are expressed, while LILRB4 is not expressed [36]. However, LILRB4 can counterregulate lipopolysaccharide-mediated inflammation in several neutrophil-dependent acute effector phases [37], which means that LILRB4 contributes to the inhibition of neutrophil-dependent inflammation in vitro [38]. Furthermore, under normal physiological conditions, LILRB4 suppresses the lipopolysaccharide-induced increase in intravascular neutrophil adhesion, which provides critical innate protection against an excessive pathologic response to a bacterial component [39].

Dendritic cells

DCs are the only immune cells that can induce primary immune responses, and they can also permit the formation of immunological memory [40], as well as maintain the balance between tolerance and immunity [41]. Immature DCs have been shown to have the ability to reduce antigen stimulation [42], and mature dendritic cells are the most potent and efficient APCs [5, 43], which suggests that the tolerance-inducing potential of DCs is related to their maturation status [44]. The differential expression of LILRB4 during the maturation of DCs suggests

an important role of LILRB4 in promoting DC maturation [45].

LILRB4 expression on DCs influences the development of diseases. Overexpression of LILRB4 can inhibit the transcription of NF-κB-dependent genes that encode costimulatory molecules (CD80 and CD86) in DCs. As inflammation and apoptosis mostly induced through NF-κB signaling, overexpression of LILRB4 can inhibit them. In addition, the differentiation of CD8 T or CD4 single-positive T cells is not possible [46-48].

In the context of protective adaptive immunity and inflammation, in response to Salmonella infection or Toll-like receptor stimulation with Salmonella components, LILRB4 expression on DCs and macrophages is upregulated, which suggests that LILRB4 plays a physiologic role in limiting the inflammatory response during infection [46].

In addition, in regard to pathologic adaptive immunity and inflammation, LILRB4 also plays a significant role. For example, in lipopolysaccharide-mediated inflammation [37], which upregulates LILRB4 expression on human DCs [49], LILRB4 is important during the immune responses. There are two kinds of mechanisms. In one mechanism, LILRB4 weakens the ability of DCs by affecting the number of mature dendritic cells and attendant IL-4-producing lymphocytes in lymph nodes, which is a key molecule needed for DC migration. For example, LILRB4 can elicit pathologic Th2 pulmonary inflammation [27, 37]. In addition, it has been shown that LILRB4 can counterregulate the development of pathologic adaptive immune responses initiated by an innate immune signal; when left unchecked, these types of responses make a harmless and tolerizing molecule immunogenic which represents a critical step in the development of allergic airway disease [37]. Another mechanism suggests that LILRB4 may regulate the transformation of the innate response into an adaptive response by inhibiting cell chemotaxis. It has been shown that ITIM-bearing receptors can play inhibitory roles by downregulating the expression of both stromal chemokines and their cognate receptors on immune cells, which leads to attenuated cell migration and pathologic allergic inflammation. In this way, LILRB4 inhibits chemotaxis and migration of DCs from the lung to second-

ary lymphoid tissue, which downregulates DC-T cell interactions to suppress this kind of inflammation (**Figure 2**) [27].

However, the mechanism still needs to be studied. In some diseases, although LILRB4 expression is upregulated, the tolerogenic role of LILRB4 has not be shown, and the reasons for this remain unknown. For example, in SLE, LILRB4 cannot play an effective role. One study showed that the type I interferon (IFN) pathway participates in the pathogenesis of SLE, and IFNs can induce LILRB4 expression by plasmacytoid DCs and mature dendritic cells [18].

Macrophages

Macrophages are the main immune cells located in the lung tissue [38]. LILRB4 ligation changes the cytokine secretion profile of macrophages, and it also leads to an upregulation of IL-10 secretion by in vitro-cultured macrophages. In addition, it reduces the expression of the strongly inflammatory chemokine IL-8 [15].

LILRB4 and LILRB5 can activate the JAK/STAT signaling pathway and control the expression of cytokines in macrophages. They also induce the expression of chemokines and Th1, Th2, and Th17 cytokines, which suggests that they are innate immune receptors related to SHP-2, MHC class I, and beta 2-microglobulin [50, 51].

Monocytes

Depending on the nature of the stimuli and the position of the tyrosine residue in LILRB4 ITIMs, LILRB4 may have complex inhibitory and activating effects on monocytes [10].

Through triggering dephosphorylation of key signaling proteins, LILRB4 inhibits FcγRI-mediated cytokine production and regulates endocytosis/phagocytosis on monocytes [52].

Silencing of LILRB4 in monocyte-derived dendritic cells potentiates stimulus-induced release of chemokines, which may be involved in T cell trafficking to the CNS [53].

B cells

LILRB4 is not expressed on normal B cells [54]. However, in memory B cells, gp49b, the mouse counterpart of LILRB4, suppresses the devel-
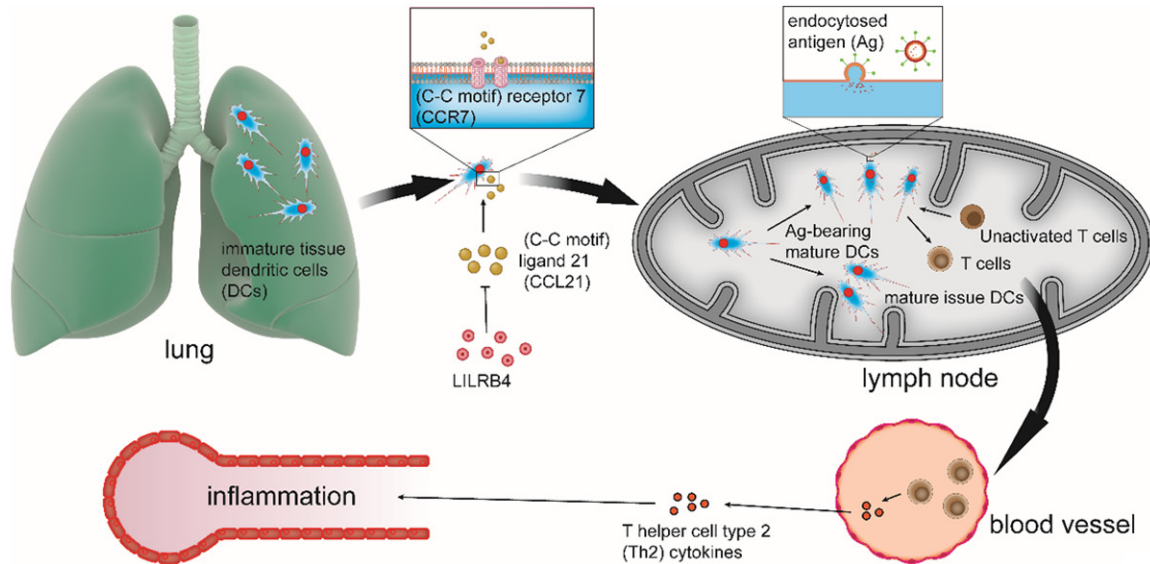
Figure 2. LILRB4 inhibits chemotaxis and migration of DCs from the lung to secondary lymphoid tissues. In the context of pulmonary allergic inflammation, immature tissue dendritic cells (DCs) go through an innate immune maturation process. During this process, mature issue DCs will migrate from the lung to tissue-draining lymph nodes (LNs), which is mediated by chemokine (C-C motif) receptor 7 (CCR7), the only receptor of chemokine (C-C motif) ligand 21 (CCL21). In addition, some mature DCs degrade endocytosed antigen (Ag) and turn into Ag-bearing mature DCs. Ag-bearing mature DCs attract and activate cognate Ag-specific T cells, which leads to their proliferation, polarization, and migration from the LNs to the blood. At the same time, Ag-bearing mature DCs generate Th2 cytokines. Th2 cytokines can migrate to target tissues, where they can lead to pathologic adaptive immune inflammation. The function of LILRB4 is to downregulate the expression of CCL21 to inhibit chemotaxis and migration of DCs from the lung to secondary lymphoid tissues, which can suppress inflammation.

opment of marginal zone B cells, memory B cells and Ab production to prevent excessive IgE production, which would otherwise lead to allergic diseases [1, 55]. In addition, in some diseases, such as pulmonary embolism, LILRB4 expression is upregulated [56], suggesting that LILRB4 plays a role in the immune response in B cells.

Natural killer (NK) cells

NK cells express inhibitory receptors, which recognize distinct 'self' class I molecules of the major histocompatibility complex, and in addition, NK cells can lyse tumor or virus-infected cells [57]. In human NK cells, a family of ITIM-bearing receptors called killer cell Ig-like receptor (KIRs) are expressed. KIRs have significant sequence homology with LILRB4 and can recognize MHC class I allotypes. A chimeric receptor consisting of the extracellular and transmembrane domains of a human KIR is expressed on NK cells from humans infected with cytomegalovirus or lymphocytic choriomeningitis virus [58]. After infection with vaccinia virus, LILRB4 expression is elicited on NK cells and T cells [59].

Mast cells

Mast cells participate in many physiological mechanisms and play a significant role in antimicrobial defense [14].

LILRB4 inhibits IgE-dependent activation of mast cells in vitro through its ITIMs, which recruit src homology domain type-2-containing tyrosine phosphatase 1 to the cell membrane. In addition, LILRB4 could counterregulate the shock induced during active systemic anaphylaxis, which is probably elicited by inhibition of FcR-induced mast cell degranulation. Furthermore, for mast cells, stem cell factor is an essential growth and survival factor [39], which has the ability to activate mast cells [60].

Microglia

Microglia are immune cells of the CNS, and LILRB4 expression increases when microglia participate in the immune response [61]. CD11c-positive microglia, which represent 23% of all activated microglia, play a role in the inflammatory response in the context of Alzheimer's disease [62].

Immunologically active substances

Interleukins (ILs)

IL-10 is a kind of anti-inflammatory cytokine [63], and it has immune-stimulating and immunosuppressive dual biological functions [64]. As IL-10 can upregulate LILRB1, LILRB2, LILRB3 and LILRB4 on APCs, IL-10 is an inhibitory cytokine that may result in a feedback loop of LILR-mediated inhibition. This means that IL-10 is an effective anti-inflammatory factor [15].

For DCs, one kind of IL-10-producing DC called DC-10 has been identified in the human body and secretes high levels of IL-10 [65]. In addition, DCs treated with resveratrol are more effective in producing IL-10 than untreated DCs [66].

Pathological role of LILRB4

LILRB4 is considered to be an inhibitor of T cell activation in transplantation, autoimmunity and allergy [67] and has obvious differential expression in many kinds of immune-related diseases. As such, research on the pathological role of LILRB4 is valuable and important.

Tumors

In patients with malignant tumors, LILRB4 inhibits CD4+ Th cell proliferation by binding to the ligand CD166 (activated leukocyte adhesion molecule) and CD8+CD28- T cell production and promotes tumor growth and tumor infiltration [24, 68-71]. In 2019, Tomic, S. et al. showed that prostaglandin E2 could induce different subpopulations of Treg cells through effects of LILRB4 on myeloid-derived suppressor cells, a major cell type driving tumor progression, by using a protocol for the generation of mononuclear (M)-MDSCs [72]. It should be noted that the ability of LILRB4 to induce cancer stem cell (CSC) differentiation into macrophages has been proven by follow-up studies, which implies a connection to the tumor microenvironment [73]. A recent study has shown that LILRB4 plays an essential role during tyramine and tyramine receptor (TyrR) activation [74]. Given its emerging role in tumorigenesis, this finding highlights the relationship between LILRB4 and tumors [75].

In addition to inducing tumorigenesis, in the development of tumors, the expression of LIL-RB4 may induce immunosuppression and affect the survival rate of patients. For example, by comparing peripheral blood monocytes in samples from 105 patients with non-small-cell lung cancer and 20 controls, de Goeje, P. L. et al. found that the expression of LILRB4 on myeloid-derived suppressor cells is associated with decreased survival in patients with non-small-cell lung cancer [28, 76]. In serum cytokine mediator analysis in hepatocellular carcinoma samples, the serum levels of LILRB4 in patients with hepatocellular carcinoma were significantly higher than those in patients in the control group [77]. High levels of LILRB4 may have some association with tumor development. As early as 2007, an experimental study using a humanized severe combined immunodeficiency (SCID) animal model by Cortesini, R. et al. has shown that LILRB4 depletion or blockade in patients with pancreatic cancer is crucial to the success of immunotherapy [78]. In the immune escape of tumor cells, the expression of LILRB4 may affect the sensitizing activity of antigen-presenting cells and is therefore the cause of the failure of interventions to enhance the immune response of patients to malignant tumors such as gastric cancer and pancreatic cancer [79]. In terms of specific intervention pathways, there is growing evidence that LILRB4 may be involved in the regulation of tumor progression by inhibiting the Akt pathway; therefore, LILRB4 has been identified as a marker for malignancy [80, 81] (**Figure 3**).

However, the expression of LILRB4 does not necessarily contribute to the development of tumors. Studies by Park, M. et al. indicate that LILRB4 may have dual inhibitory and activating functions depending on the location and/or stimulatory nature of functional tyrosine residues in ITIMs [10]. Si, Y. Q. et al. also found that LILRB4 was upregulated during the killing of tumor cells by cyclosporine [2]. Schmid, A. S. et al. constructed an antibody fusion protein that enhances neutrophil activity by using granulocyte colony-stimulating factor and LILRB4 as payloads. The results of animal experiments show that this novel fusion protein can be expressed and efficiently delivered to the tumor site and kill tumor cells [82] (**Figure 3**).

Leukemia

LILRB4 expression is acquired at an early stage by normal myelomonocytic precursors [83].
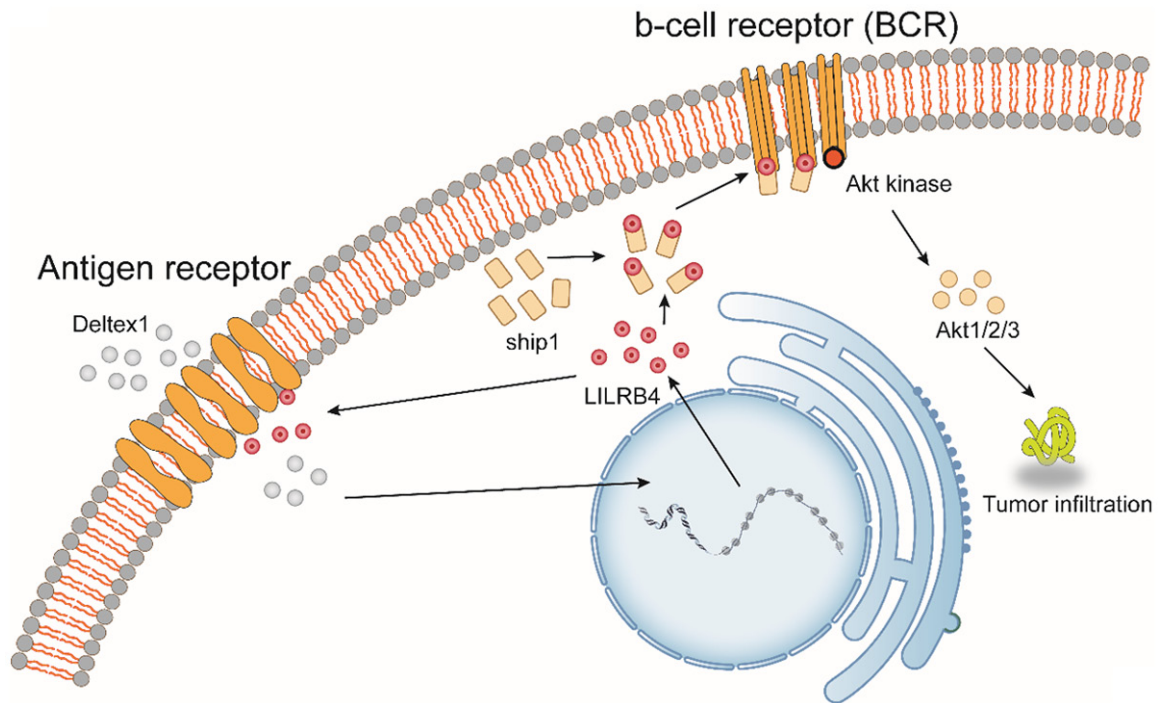
Figure 3. Dual role of LILRB4 during tumorigenesis. LILRB4 has dual effects in cancer. On the one hand, immune cells escape from tumor cells by affecting the activity of antigen-presenting cells; on the other hand, LILRB4 expression is upregulated under the action of the lymphocyte antigen receptor signal inhibitor Deltex1. A large amount of LILRB4 interacts with phosphatidylinositol-3,4,5-triphosphate 5-phosphatase 1 on the cell surface to inhibit the activity of Akt kinase. Decreased Akt kinase activity affects the downstream Akt pathway, which in turn inhibits tumor invasion.

Pathological changes in bone marrow cells often lead to the occurrence of leukemia. In this process, the expression of LILRB4 is worth exploring.

Multiple studies have shown that the expression of LILRB4 in single AML cells was higher than that in normal cells [84], and the expression of LILRB4 was negatively correlated with the overall survival of AML patients [13, 80, 83]. In patients with AML, LILRB4 inhibits T cell activation by upregulating the expression of various T cell inhibitors, such as BCL6, and promotes the development of AML [83, 85, 86]. In addition, the interleukin-2 receptor, 1,25-dihydroxyvitamin D alpha chain (CD25), on AML cells may capture environmental IL-2 and deliver it to peripheral T lymphocytes, resulting in the production of LILRB4 as a growth stimulus for CD25-positive AML cells [87].

During AML cell migration, apolipoprotein E binds AML cells that have infiltrated the tissue through LILRB4, which activates a downstream signaling pathway in combination with T cell suppression and tumor infiltration [25]. Deng, M. et al. employed a murine tumor model and human cells and revealed that LILRB4 coordinates tumor invasion pathways in single leukemia cells by creating an immunosuppressive microenvironment [25]. In the tumor invasion pathway, miR-155 may be the main target of IL-3 signal transduction in primary AML cells. Given the increasingly obvious role of miR-155 in tumorigenesis and the upregulation of the LILRB4 receptor alpha subunit in AML, it seems reasonable to think that LILRB4 may play an important role in the transformation of leukemia [88]. Regarding the relationship between LILRB4 and tyrosine mentioned above, recent research shows that LILRB4 may influence the early pathological process in leukemia through tyrosine kinases [89], while the ITIMs of LILRB4 in AML mediate T cell suppression and AML cell migration [90].

Not only is the high expression of LILRB4 related to the occurrence and development of AML but newer research has also found that high expression of LILRB4 is also associated with

complications of AML. Kobayashi, K. et al. found a paraneoplastic hypoleukemia syndrome associated with LILRB4-IgH-positive acute lymphoblastic leukemia [91].

Currently, immunological checkpoint blockade therapy has not shown a clinical benefit in treating leukemia. Based on the studies listed above, this may be due to the presence of an immune evasion mechanism in leukemia that creates an immunosuppressive microenvironment through LILRB4 [25]. Fortunately, there are many therapeutic approaches to the treatment of AML through LILRB4, one of which is the monocyte antibody h128-3, which blocks the activation of LILRB4 and inhibits tissue infiltration of single AML cells [92]. John, S. et al. prepared a novel anti-LILRB4 CAR-T cell with high antigen affinity and specificity. These CAR-T cells exhibited highly potent effects on AML cells in vitro and in vivo, specifically targeting single AML cells and were not toxic to normal hematopoietic progenitor cells [85]. Bispecific antibodies developed for the low-affinity LILRB4 receptor CD123 can redirect immune effector cells to AML targets [93, 94]. Given its significant expression differences and pathological mechanisms during the development of AML, LILRB4 is an emerging immune target, and treatment with LILRB4 may improve therapeutic effects in AML [95].

Ectopic expression of LILRB4 in chronic lymphocytic leukemia is a prominent feature of tumor B cells and hematopoietic stem cells, and thus LILRB4 is considered to be a selective marker for chronic lymphocytic leukemias. Based on this, many targeted therapies for the treatment of chronic lymphocytic leukemia have been developed, such as combination therapies including anti-CTLA-4 and anti-LILRB4 agents [95, 96]. The LILRB4 receptor is overexpressed in CML cells compared to normal hematopoietic cells and is therefore a receptor target for cancer drug delivery systems. Bellavia, D. et al. designed a novel anticancer agent that is capable of targeting CML cells and inhibiting the growth of cancer cells in vitro and in vivo using LILRB4-containing exosomes [97].

Toxoplasma infection

The expression of LILRB4 is also associated with the outcome of pregnancy. LILRB4 is a central inhibitory receptor of uterine dendritic cells and plays an important immunomodulatory role at the maternal-fetal interface. Infection with Toxoplasma gondii during early pregnancy can cause malformations such as miscarriage and fetal death. Later studies found that the expression levels of functional LILRB4 molecules in the membrane, arginine metabolizing enzymes and related cytokines were abnormal in Toxoplasma gondii infection models, demonstrating that Toxoplasma infection can downregulate LILRB4 in decidual macrophages [98]. Downregulation of LILRB4 enhances M1 macrophage activation and attenuates M2 macrophage tolerance by altering the expression of M1- and M2-related membrane molecules, the synthesis of arginine metabolizing enzymes, and the secretion profile of cytokines. C. H. et al. found that the LILRB4 rs-40401 polymorphism was associated with an increased risk of miscarriage in patients undergoing in vitro fertilization by analyzing single nucleotide polymorphisms [99]. A reduction in LILRB4 can regulate the expression of functional molecules (CD80, CD86, HLA-DR or MHC class II) on uterine dendritic cells after infection with Toxoplasma gondii, leading to abnormal pregnancy outcomes [17].

Immune disease

Abnormal expression of LILRB4 may trigger immune-related diseases [100, 101]. A large number of animal models show that LILRB4 induces the secretion of proinflammatory cytokines by T cells and B cells, reduces the expression of IL-10 by B cells, and plays an important role in T cell- and B cell-mediated autoimmune diseases (such as SLE) [102]. In autoimmune responses, self-reactive CD4+ T cells can promote effector inflammation and injury through LILRB4-dependent amplification loops, while autoreactive LILRB4+CD4+ T cells accumulating in effector organs stimulate LILRB4+ tissue macrophages to produce systemic chemokines that attract single cells. The newly recruited monocytes differentiate into antigen-presenting cells, stimulating local LILRB4+CD4+ T cell proliferation, thereby amplifying inflammation [103].

Kawasaki disease is an acute systemic vasculitis syndrome that occurs in children and is associated with secretory cells (ASCs) that highly express LILRB4 [46].

SLE is an autoimmune disease. Animal experiments by Wong, Y. L. et al. showed that mouse glycoprotein 49B (gp49B), which corresponds to human LILRB4, is a pathogenic element in SLE [1]. Clinically, in plasma cells from SLE patients, the expression of leukocyte immunoglobulin-like receptor (LILR) B4 is enhanced [104, 105]. For these patients with SLE, the enlarged population size of stromal plasma cells and plasma cells with enhanced LILRB4 expression is a characteristic of untreated SLE [18]. Therefore, LILRB4 may be used as a new molecular marker to identify pathogenic cells in SLE.

LILRB4 also plays a very important role in the pathological development of various inflammatory diseases. For example, LILRB4 is downregulated in stress-exposed hearts in patient and mice, and mice with LILRB4 knockout develop cardiac hypertrophy and heart failure via promotion of cardiac dysfunction, fibrosis, inflammation, and apoptosis [47, 106, 107]. During the pathological process of atherosclerosis, the lack of LILRB4 significantly accelerates the development of atherosclerotic lesions by reducing the phosphorylation level of SHP1, leading to characteristic increased lipid infiltration and decreased collagen content [108]. In addition, LILRB4 is also associated with the development of nonalcoholic fatty liver disease (NAFLD) [109]. Evidence suggests that the lack of LILRB4 can also aggravate many inflammatory respiratory diseases, such as acute lung injury and asthma, through the NF-kappaB and p38-MAPK signaling pathways [107, 110, 111]. In addition, high expression of LILRB4 correlates with high mortality in patients with pulmonary tuberculosis (PTB) [112]. Furthermore, a recent transcriptome sequencing and whole-genome expression profiling analysis of pulmonary inflammation in an MWCNT-induced mouse model revealed novel crosstalk between downregulation of LILRB4 and regulation of immunoreactivity genes such as Cd72 in the process of lung inflammation [113] (**Figure 4**). Therefore, targeting LILRB4 to promote its expression or activation is a promising strategy for the treatment of systemic inflammatory and metabolic diseases. Notably, recent studies have identified that LILRB4 is overexpressed in monocytes from HIV patients [114]. It is highly likely that LILRB4 can affect the pathological process of HIV, albeit experimental evidence is lacking at present.

Upregulated expression of LILRB4 has also been found in the treatment of immune diseases. For example, LILRB4 and ILT4 are involved in the regulation of the immune response to multiple sclerosis via interferon and vitamin D [26]. High LILRB4 levels in sepsis patients were independently associated with hospital mortality; therefore, they could be used to predict prognosis in patients with sepsis [115].

The differential expression of LILRB4 in infectious diseases makes it an important biomarker for predicting latent infections. Studies by La Manna, M. P. et al. featured the Luminex Bead Array Multiplex Immunoassay and showed that LILRB4 was significantly higher in the active tuberculosis and long-term tuberculosis groups than in the nontuberculosis group [116]. Consistent with this, high expression of LILRB4 in patients with gram-negative bacterial bloodstream infection was observed, which shows the potential utility for GN-BSI biomarkers [117].

Mental illness

Mounting evidence suggests that LILRB4 signaling may be involved in the pathophysiological process of schizophrenia. For example, LILRB4 was significantly negatively correlated with the immediate memory index in patients with chronic drug-induced schizophrenia, suggesting that IL-3 may be involved in the loss of immediate memory in the chronic phase of schizophrenia [118, 119].

Multiple sclerosis is the most common type of central nervous system demyelinating disease. IFN beta can induce the expression of LILRB2 and LILRB4 on monocytes, and this increased expression can be found in patients with relapsing-remitting multiple sclerosis who are treated with IFN beta. In addition, it has been reported that the effect of IFN beta on these immunomodulatory molecules and monocyte immunobiology is selective [26]. It has been shown that vitamin D and IFN beta can act together to modulate some disease activities [120]. One studied showed that $1\alpha,25(OH)_2$ D3 could effectively induce LILRB4 on APCs [121], and IFN beta and $1\alpha,25(OH)_2$ D3 could work together to induce LILRB4 expression on monocytes. As a result, vitamin D cotreatment could have beneficial effects on disease-modifying drugs. Interestingly, IFN beta and $1\alpha,25(OH)_2$
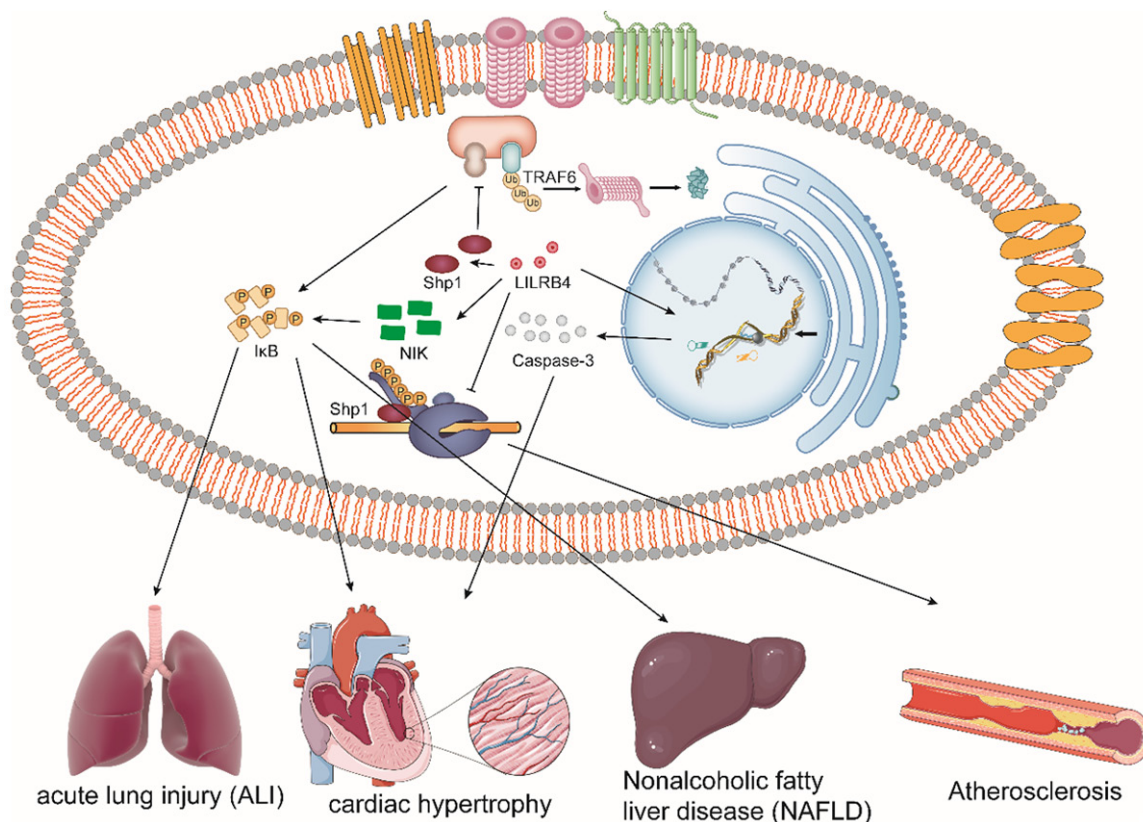
Figure 4. The role of LILRB4 in the development of various diseases. The expression of LILRB4 affects the development of various immune diseases. For example, LILRB4 deficiency plays a detrimental role in the activation of macrophages (BMDMs) associated with acute lung injury by promoting the NF-kappaB signaling pathway. The loss of LILRB4 accelerates cardiac hypertrophy by promoting upregulation of caspase-3 activation via the nuclear factor kappaB (NF-kappaB) signaling pathway. LILRB4 inhibits the ubiquitination of TRAF6 by recruiting SHP1, which largely reverses nonalcoholic fatty liver disease (NAFLD). LILRB4 deficiency promotes atherogenesis by reducing Shp1 phosphorylation.

D3 have the opposite effects on LILRB2 expression on monocytes, which means that IFN beta can be beneficial for the tolerogenic properties of these cells by counteracting the effects of $1\alpha,25(OH)_2$ D3 on LILRB2 expression. This indicates that LILRB4 may be used as an immunomodulator in autoimmune diseases, which is beneficial for autoimmune disease therapy [26].

Furthermore, it is presumed that LILRB4 also participates in the basic mechanisms of CNS immune surveillance [26]. Silencing of LILRB4 in monocyte-derived dendritic cells potentiates stimulus-induced release of chemokines, which may be involved in T cell trafficking to the CNS [53].

Conclusions

Current studies have found that LILRB4 is differentially expressed in a variety of diseases, indicating that there is great potential for physi-

ological and pathological studies of LILRB4. Some treatments targeting LILRB4 have been attempted, but there is still much room for research on LILRB4. Important research areas that need to be addressed include increasing our understanding of the underlying pathological mechanisms involving LILRB4 at the cellular and molecular levels. LILRB4 has been used as a new biomarker to assess disease activity and achieve early screening and assessment.

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Disclosure of conflict of interest

None.

Abbreviations

LILR, leukocyte immunoglobulin-like receptor; IL, interleukin; MHC, major histocompatibility complex; ITIM, immunoreceptor tyrosine-based inhibitory motif; APC, antigen-presenting cell; SLE, systemic lupus erythematosus; NF-kappa B, nuclear factor-kappa B; SHP, phosphatase; AML, acute myeloid leukaemia; CNS, central nervous system; Th, T helper cell; Treg, regulatory T; DC, dendritic cell; IFN, interferon; NK, natural killer; KIR, killer cell Ig-like receptor; IL, interleukin; CD25, interleukin-2 receptor alpha chain; NAFLD, Nonalcoholic fatty liver disease.

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