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REVIEW

CANCER INNOVATION

Leukocyte immunoglobulin-like receptor B4: A keystone in immune modulation and therapeutic target in cancer and beyond

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Abstract

Leukocyte immunoglobulin-like receptor B4 (LILRB4) significantly impacts immune regulation and the pathogenesis and progression of various cancers. This review discusses LILRB4's structural attributes, expression patterns in immune cells, and molecular mechanisms in modulating immune responses. We describe the influence of LILRB4 on T cells, dendritic cells, NK cells, and macrophages, and its dual role in stimulating and suppressing immune activities. The review discusses the current research on LILRB4's involvement in acute myeloid leukemia, chronic lymphocytic leukemia, and solid tumors, such as colorectal cancer, pancreatic cancer, non-small cell lung cancer, hepatocellular carcinoma, and extramedullary multiple myeloma. The review also describes LILRB4's role in autoimmune disorders, infectious diseases, and other conditions. We evaluate the recent advancements in targeting LILRB4 using monoclonal antibodies and peptide inhibitors and their therapeutic potential in cancer treatment. Together, these studies underscore the need for

Abbreviations: AD, alzheimer's disease; AG490, JAK2 inhibitor; ALI, acute lung injury; AML, acute myeloid leukemia; ApoE, apolipoprotein E; ARG1, arginase-1; Aβ, amyloid-β; CAR-T cells, chimeric antigen receptor T cells; CD166, cluster of differentiation 166; CD85k, cluster of differentiation 85k; CLL, chronic lymphocytic leukemia; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CTGF, connective tissue growth factor; DEGs, differentially expressed genes; DFS, disease-free survival; ECM, extracellular matrix; FN, fibronectin; HASMCs, human aortic smooth muscle cells; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; HLA-G, human leukocyte antigen G; IBD, inflammatory bowel disease; IL, interleukin; ILT3, immunoglobulin-like transcript 3; ILT3-Fc, immunoglobulin-like transcript 3 - Fc; IM, intrapulmonary metastasis; ITIMs, immunoreceptor tyrosine-based inhibitory motifs; JAK2, janus kinase 2; KD, kawasaki disease; LILRB4, leukocyte immunoglobulin-like receptor B4; LILRs, leukocyte immunoglobulin-like receptors; LIR5, leukocyte immunoglobulin-like receptor 5; mAb, monoclonal antibody; MD, molecular dynamics; MDSCs, myeloid-derived suppressor cells; MMP2, matrix metalloproteinase 2; MPLC, multiple primary lung cancers; NAFLD, nonalcoholic fatty liver disease; NFκB, nuclear factor kappa B; NK cells, natural killer cells; NSCLC, non-small cell lung cancer; PCH, pathological cardiac hypertrophy; PIR-B, paired immunoglobulin-like type 2 receptor beta; RELT, receptor expressed in lymphoid tissues; SHP-1, src homology 2 domain-containing protein tyrosine phosphatase 1; SHP-2, src homology 2 domain-containing protein tyrosine phosphatase 2; SLE, systemic lupus erythematosus; SM22α, smooth muscle 22 alpha; STAT3, signal transducer and activator of transcription 3; STAT6, signal transducer and activator of transcription 6; T cells, effector T cells; TAMs, tumor-associated macrophages; Th cells, T helper cells; TME, tumor microenvironment; uPAR, Urokinase-type plasminogen activator receptor; α-SMA, alpha-smooth muscle actin; αVβ3, integrin alpha V beta3.

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further research on LILRB4's interactions in the tumor microenvironment and highlight its importance as a therapeutic target in oncology and for future clinical innovations.

KEYWORDS
cancer therapy, immune checkpoint, immunotherapy, leukocyte immunoglobulin-like receptor B4, monoclonal antibodies

1 | INTRODUCTION

Leukocyte immunoglobulin-like receptor B4 (LILRB4) is a myeloid inhibitory receptor that is a member of the family of leukocyte immunoglobulin-like receptors (LILRs) and plays a pivotal role in the regulation of immune tolerance. The exploration of LILRB4, also known as immunoglobulin-like transcript 3 (ILT3)/leukocyte immunoglobulin-like receptor 5 (LIR5)/cluster of differentiation 85k (CD85k) and gp49B in mice [1, 2], has significantly advanced our understanding of the complex mechanisms underlying immune regulation. As an integral member of the LILRB family [3], LILRB4 plays a pivotal role in both innate and adaptive immunity and has, thus, been an important focus in the expansive field of immunological research [4]. This review aims to consolidate current knowledge of LILRB4, with a focus on its structural characteristics, expression across various immune cells, functional interactions with diverse ligands, and its comprehensive impact on disease pathogenesis and therapeutic possibilities.

Recent insights into LILRB4's expression and function within the tumor microenvironment have indicated that LILRB4 may represent a novel therapeutic target in oncology. By modulating the interaction between cancer cells and the immune system, LILRB4 contributes to tumor immune evasion, a key hurdle in effective cancer therapy. This critical immune suppression within the cancer milieu has made LILRB4 a compelling target for therapeutic intervention. LILRB4 was initially identified in macrophages [5], and subsequent studies revealed its extensive expression throughout multiple immune cell types, including dendritic cells, monocytes, B cells, natural killer (NK) cells, T cells, and osteoclasts. This wide-ranging expression underlines the versatile role of LILRB4 in the dynamics of the immune system [6–9], extending its implications to cancer biology, where its inhibitory pathways can influence tumor progression and response to therapy.

In this review, we analyze the molecular mechanisms of LILRB4, its interactions with immune cells, and the implications these interactions have in various diseases, with a particular emphasis on cancer (Figure 1). This highlights its critical role in modulating immune responses, pivotal in the context of tumor immunology, and autoimmune disorders. We further discuss the translation of LILRB4 research to therapeutic strategies, especially in the realm of biologics, where monoclonal antibodies and peptide inhibitors targeting LILRB4 represent a frontier in innovative cancer therapy approaches. This highlights not only the therapeutic potential of targeting LILRB4 but also its

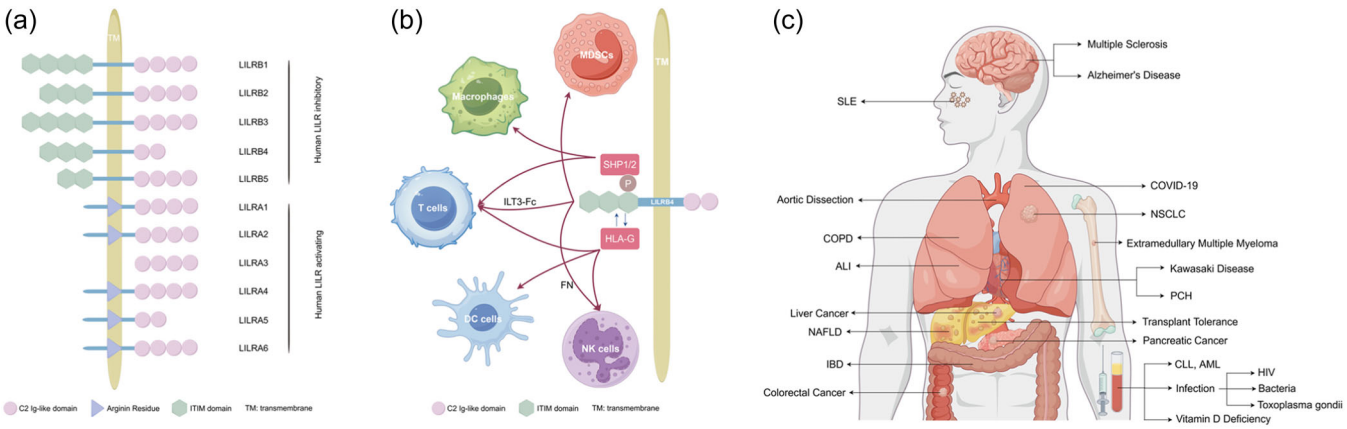

FIGURE 1 Structure and function of LILRB4. (a) Structure of LILRs. (b) Interaction of LILRB4 with Immune Cells. (c) Role of LILRB4 in Different Diseases. *Copyright information: (a) FigDraw, ID OIPTUdd4d7. (b) and (c) FigDraw, ID YWORIff407.*

significance as a bridge between fundamental immunology and clinical oncology, offering new avenues for the management of immune-mediated conditions and cancer treatment.

2 | LILRB4 STRUCTURE AND EXPRESSION

LILRB4 contains extracellular immunoglobulin-like domains, a transmembrane region, and a cytoplasmic tail. The extracellular portion of LILRB4 consists of two to four immunoglobulin-like domains that are responsible for ligand binding. The transmembrane region anchors the receptor to the cell membrane, while the cytoplasmic tail contains immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that are crucial for its signaling functions. LILRB4 primarily mediates suppressive immune responses by transmitting inhibitory signals through its ITIMs [10].

LILRB4 expression is regulated by IL-10-induced phosphorylation of signal transducer and activator of transcription 3 (STAT3) in human endothelial cells [11]. Upon binding to its various ligands, including CD166 [12], integrin αVβ3 [13], apolipoprotein E [14], and fibronectin [15, 16], LILRB4 recruits SHP-1 and SHP-2; these phosphatases then dephosphorylate tyrosine-phosphorylated proteins, effectively suppressing activation signals [17, 18]. Through this mechanism, LILRB4 transmits inhibitory signals that modulate immune cell activation and immune responses [17]. SHP-2 interacts with the ITIMs of LILRB4 to initiate LILRB4 phosphorylation, leading to STAT6 activation and the accumulation of phosphorylated STAT6 in macrophage nuclei, thus regulating arginase-1 [19–21]. Notably, LILRB4 exhibits both inhibitory and activating functions, contingent on the specific tyrosine residues within its ITIMs, with Tyr389 mediating inhibitory signals and Tyr337 promoting activating signals, thus playing a complex regulatory role in immune responses [22].

LILRB4 induces effector T cell dysfunction and promotes T suppressor cell differentiation, indicating the therapeutic potential of LILRB4 for modulating excessive immune responses, particularly in autoimmune diseases or the induction of transplant tolerance [14]. Additionally, through modulation of LILRB4, the immune system responsiveness can be adjusted [10], indicating that LILRB4 may have a significant role in areas such as cancer treatment. Thus, LILRB4 has emerged as a key player in autoimmune diseases, transplant tolerance induction, and other conditions [10].

3 | MECHANISMS OF LILRB4 IN IMMUNE REGULATION

LILIRB4 interacts with human leukocyte antigen G (HLA-G) [23] and plays a significant role in diminishing immune cell activation, particularly affecting NK and T cells. This indicates LILRB4's capacity to orchestrate immune responses across a spectrum of cell types.

Recent studies have revealed the role of LILRB4 in T cell immunology. Key findings by Kim-Schulze et al. [24] and Chang et al. [25] demonstrated LILRB4's involvement in modulating T cell responses, notably through ILT3-Fc. The interaction of LILRB4 and ILT3-Fc promotes Th hypersensitivity and CD8+T suppressor cell differentiation, reshaping T cell dynamics. LILRB4 also regulates pro-inflammatory cytokine expression and T cell migration, integral to immune responses. ILT3-Fc induces T suppressor cell differentiation for immune balance [26], and controls inflammatory microRNA transcription, essential for CD8+T suppressor cell differentiation [27]. Another study showed the effect of membrane-bound and soluble ILT3 in triggering antigen-specific T suppressor cells, expanding our understanding of LILRB4's regulatory function [28].

Studies by Manavalan et al. [29] and Penna et al. [30] showed that LILRB4 expression correlates with a tolerogenic state in dendritic cells, hinting at its significance in fostering immune tolerance. Zhou et al. demonstrated the importance of LILRB4 in transplant tolerance, particularly through its role in the induction of tolerogenic dendritic cells mediated by membrane-bound HLA-G [31]. LILRB4 has also been demonstrated as a key regulator in maintaining the equilibrium between immune activation and tolerance [32] and plays a crucial role under tryptophan-deprived conditions, aiding in the induction of regulatory T cells [33]. Another study showed the rapamycin-induced upregulation of ILT3 on dendritic cells [34], enhancing our understanding of its immunoregulatory pathways.

The interaction of LILRB4 with fibronectin (FN), which leads to the attenuation of NK cell natural cytotoxicity, was reported by Itagaki et al. [35]. This finding revealed an unexpected role for LILRB4 in dampening NK cell activity, especially within the tumor microenvironment.

The impact of LILRB4 on myeloid-derived suppressor cells and macrophages has been extensively studied. Su et al. [36] and Singh et al. [37] demonstrated that LILRB4 regulates myeloid-derived suppressor cells, influencing their polarization and impact on tumor metastasis. Sharma et al. [38] reported the pronounced expression of LILRB4 on tumor-associated macrophages, suggesting that targeting LILRB4 could alleviate their suppressive effects and potentially enhance cancer immunotherapy strategies.

4 | LILRB4 IN CANCER

4.1 | Leukemia

In leukemia research, LILRB4 also referred to as ILT3, has been shown to have a multifaceted impact on disease progression and immune evasion. LILRB4 has emerged as a novel potential immune checkpoint, drawing significant interest for its unique role in cancer progression and immune evasion. In chronic lymphocytic leukemia research, Colovai et al. [39] showed that the expression of ILT3 on tumor B cells is intricately linked with lymphoid organ involvement, suggesting a pivotal role in the disease's systemic spread. Concurrently, Zurli et al. [40] provided insights into ILT3's regulatory function in cell signaling pathways, notably its capacity to modulate Akt kinase activation. This regulatory mechanism is crucial, as Akt signaling plays a central role in cell survival and proliferation, underlining the potential of targeting ILT3 for therapeutic intervention.

ILT3 also plays a key role in AML. LILRB4 has been identified as playing a key role in promoting tumor growth, aiding leukemia cell infiltration, and impairing T-cell function. These activities in leukemia are mediated through the apolipoprotein E (ApoE)/LILRB4/SHP-2/nuclear factor kappa B (NF-κB)/urokinase-type plasminogen activator receptor (uPAR)/arginase-1 (ARG1) signaling axis [14, 41]. The external presentation of ApoE activates LILRB4 on monocytic AML cells, leading to the subsequent activation of SHP-2 and NF-κB [14, 41, 42]. This pathway not only inhibits T-cell proliferation but also facilitates tissue infiltration [14]. Studies by Dobrowolska et al. [43] and others [14, 41, 44] have shed light on ILT3's role as a differentiation marker, significantly influencing leukemic cell behavior and interaction with the immune system. These findings indicate that LILRB4, both in tumor cells and within the tumor microenvironment, plays key roles in modulating the immune system's ability to recognize and combat cancer cells.

Cutting-edge anti-LILRB4 chimeric antigen receptor T cell therapies have demonstrated efficacy in halting the progression of AML [14, 44]. These innovative therapies target LILRB4 directly, disrupting its immunosuppressive functions, and thereby enhancing T cell-mediated cytotoxicity against leukemic cells. Furthermore, the advancement of anti-LILRB4 antibody-drug conjugates has marked a significant milestone in AML treatment strategies [45]. This approach harnesses the specificity of monoclonal antibodies to deliver cytotoxic agents directly to cancer cells, minimizing harm to healthy tissues, as researched by Li et al. [46]. The following studies have expanded our understanding of LILRB4's role in immune modulation and leukemia progression. Su et al. [47] found that inhibiting FTO reduces LILRB4 expression, sensitizing leukemia cells to T cell cytotoxicity, and overcoming immune evasion. Bergstrom et al. [48] demonstrated that LILRB4 is associated with CNS infiltration in AML patients, suggesting a role in disease dissemination. Zhao et al. [49] revealed that PRMT5 promotes AML cell migration by upregulating LILRB4 through the mTOR pathway, enhancing the invasive capacity of leukemic cells. Churchill et al. [50] identified LILRB4 as a highly sensitive and specific marker for monocytic AML, highlighting its potential as a therapeutic target.

4.2 | Pancreatic cancer

In the challenging landscape of pancreatic cancer treatment, immune modulation has become a focal point for developing new therapeutic strategies. The immunosuppressive tumor microenvironment of pancreatic cancer significantly hinders the effectiveness of conventional and immunotherapeutic treatments. Thus, LILRB4 has drawn attention because of its potential impact on immune cell activity, particularly T cells, which are pivotal for antitumor immunity.

Research conducted by Cortesini [51] and further explored by Suciu-Foca et al. [52] highlighted a critical connection between LILRB4 and the impairment of T cell responses in pancreatic cancer. These studies showed that LILRB4, through its immunomodulatory effects, plays a significant role in creating an immunosuppressive milieu that enables tumor growth and metastasis by directly inhibiting T cell activation and function. This inhibition not only reduces the effectiveness of the immune system's natural tumor surveillance mechanisms but also poses a substantial barrier to therapies that rely on immune system activation to target cancer cells. The implications of these findings are profound, suggesting that targeting LILRB4 could represent a pivotal strategy in enhancing immunotherapy efficacy for pancreatic cancer.

Antagonizing LILRB4 to relieve its suppressive hold on T cells could rejuvenate the immune response against pancreatic tumor cells, potentially overcoming one of the major hurdles in treating this formidable disease. A better understanding of LILRB4 function and its pathways offers a promising avenue for developing targeted therapies that could enhance the immune response against tumors, potentially transforming cancer treatment paradigms. This approach aligns with the growing interest in immune checkpoints as therapeutic targets, where the goal is to disinhibit the immune system's capacity to fight cancer.

Developing therapies that target LILRB4 in pancreatic cancer requires a nuanced understanding of its interactions within the tumor microenvironment and its effects on various immune cell populations. By focusing on LILRB4, researchers are not only addressing a key factor in pancreatic cancer's resistance to treatment but also providing a foundation for future combination therapies that could significantly improve patient outcomes. The potential to transform pancreatic cancer treatment through LILRB4-targeted strategies underscores the importance of continued research and clinical trials in this area, aiming to unlock new possibilities for patients battling this devastating disease.

4.3 | Non-small cell lung cancer (NSCLC)

In the realm of NSCLC, an area marked by an urgent need for innovative therapeutic approaches, the exploration of immune regulatory mechanisms offers promising areas for advancement. LILRB4 has come under intense scrutiny, particularly for its contributions to the immunosuppressive tumor microenvironment, which significantly impacts the disease's progression and patient outcomes.

Research conducted by de Goeje et al. [53] shed light on the pivotal immunosuppressive functions of LILRB4 in NSCLC, revealing its substantial influence on the behavior of tumor-infiltrating immune cells. This work, along with other studies [20, 54], revealed the capacity of LILRB4 to modulate the immune landscape within lung tumors, essentially enabling cancer cells to evade immune surveillance. By interacting with various ligands and signaling pathways, LILRB4 dampens the immune response, thereby aiding tumor persistence and growth.

These studies also demonstrated the prognostic significance of LILRB4 expression in NSCLC. High levels of LILRB4 are correlated with poor patient prognoses, indicating its potential as a biomarker for disease severity and progression. This correlation not only enhances our understanding of the biological underpinnings of NSCLC but also opens up new possibilities for targeted therapeutic interventions. The identification of LILRB4 as an immune modulatory receptor highlights the intricate balance between immune activation and suppression in cancer.

Recent genomic and transcriptomic analyses of multiple primary lung cancers (MPLC) and intrapulmonary metastasis have revealed significant insights into the tumor microenvironment. LILRB4 mRNA is downregulated in MPLC compared with intrapulmonary metastasis, and this downregulation is associated with improved disease-free survival in MPLC patients. These findings suggest that LILRB4, along with other markers, could serve as a potential therapeutic target, contributing to a better prognosis by promoting an immune-activating tumor microenvironment in MPLC [55].

Together these results suggest that antagonizing LILRB4 may be a compelling strategy to counteract the tumor-promoting immunosuppression in NSCLC. Targeting LILRB4 could restore the effector functions of immune cells within the tumor microenvironment, thereby reinvigorating the immune system's ability to combat cancer. This approach aligns with the broader shift toward immunotherapy in oncology, where harnessing the power of the immune system offers a path to overcoming cancer's formidable defenses.

4.4 | Colorectal cancer

The investigation into LILRB4 expression in colorectal cancer has revealed a nuanced landscape of immune interactions and tumor progression [56]. The role of LILRB4 in immune suppression is significant in colorectal cancer, where it modulates the tumor microenvironment to facilitate growth and survival. The presence of LILRB4 on both tumor cells and within the tumor microenvironment highlights its significant influence on dampening the immune system's ability to effectively target and eliminate cancer cells.

In colorectal cancer, LILRB4 is highly expressed on macrophages in the tumor microenvironment, suggesting its involvement in immune modulation. This indicates that LILRB4 may represent a therapeutic target for modulating immune responses in colorectal cancer [57]. By counteracting LILRB4's immunosuppressive effects, it may be possible to reinvigorate the immune system's response against colorectal tumors, potentially enhancing the efficacy of immunotherapeutic approaches.

Whether LILRB4's expression represents a prognostic factor in colorectal cancer has yet to be determined, but its presence provides an opportunity to explore its potential prognostic value. Studies have yet to examine the correlation between LILRB4 levels and disease progression in colorectal cancer. Understanding this potential relationship could offer novel insights into patient stratification and risk assessment, facilitating more personalized treatment strategies. Identifying patients with high LILRB4 expression might pinpoint those who could benefit most from therapies designed to inhibit LILRB4's immunosuppressive pathways.

4.5 | Melanoma

The role of LILRB4 in melanoma, particularly its impact on tumor survival, provides a compelling case for the receptor's broader implications in cancer biology [38]. Melanoma, known for its aggressive nature and propensity for early metastasis, presents significant challenges in treatment, partly because of its adeptness at evading immune surveillance. The study highlighting LILRB4's role in extending the survival of mice implanted with melanoma cell lines underscores the potential of LILRB4 as a critical factor in melanoma's immune evasion strategies [37].

The overexpression of LILRB4 in melanoma suggests that it contributes to the creation of an immunosuppressive microenvironment, enabling melanoma cells to evade immune detection and proliferate unchecked [37]. This evasion occurs through the modulation of immune responses, particularly by suppressing the activity of T cells and other immune cells that are crucial for mounting an effective antitumor response. Given the pivotal role of the immune system in controlling tumor growth and metastasis, the ability of melanoma cells to engage LILRB4 in suppressing immune surveillance can significantly impact disease progression and patient prognosis, highlighting the potential of targeting LILRB4 as a therapeutic strategy.

Targeting LILRB4 in melanoma, therefore, is a promising strategy to enhance immunotherapy outcomes. By inhibiting LILRB4's immunosuppressive signaling, it may be possible to restore the immune system's capacity to detect and destroy melanoma cells. Such an approach not only has the potential to improve the efficacy of current immunotherapies but also provides a foundation for new directions for the development of combination therapies that can more effectively overcome melanoma's resistance to treatment.

4.6 | Liver cancer

Liver cancer is a significant global health burden because of its high incidence and mortality rates. The liver's unique immunological environment, characterized by tolerance to antigens, poses additional challenges in the effective treatment of hepatocellular carcinoma (HCC), the most common form of liver cancer.

Research by Fan et al. [58] revealed the expression of LILRB4 in immune cells associated with liver cancer, highlighting its influence on the immune system's capacity to respond to tumor cells. This expression pattern suggests that LILRB4 may play a pivotal role in modulating the immune landscape in HCC, potentially facilitating tumor growth and progression by dampening the immune response against cancer cells. Such immune evasion mechanisms are central to the pathogenesis of HCC and represent a significant barrier to effective therapy.

4.7 | Extramedullary multiple myeloma

In the specialized field of hematology, extramedullary multiple myeloma is a particularly aggressive and challenging disease and is characterized by the spread of myeloma cells beyond the bone marrow into other parts of the body. This extramedullary progression is often associated with a poor prognosis, underscoring the need for innovative therapeutic strategies.

Sun et al. [59] reported the pathophysiological role of LILRB4 in facilitating the metastasis and cellular migration associated with extramedullary multiple myeloma. The authors further demonstrated the efficacy of targeting LILRB4 to inhibit these processes. Their study not only sheds light on the underlying mechanisms that drive the aggressive behavior of myeloma cells in an extramedullary context but also highlights LILRB4 as a novel therapeutic target. The ability to interfere with LILRB4-mediated signaling pathways offers a strategic approach to limiting the spread of myeloma cells, potentially improving patient outcomes by curtailing the progression of the disease.

Further research by Wang et al. [60] highlighted the role of LILRB4 in promoting osteolytic bone lesions in multiple myeloma. This study has shown that LILRB4 is highly expressed in multiple myeloma cells and that higher expression levels correlate with more severe bone lesions in patients. The underlying mechanism involves the p-SHP2/NF-κB/RELT signaling pathway, where LILRB4 promotes the differentiation and maturation of osteoclasts by secreting RELT. In various xenograft and patient-derived xenograft models, deletion of LILRB4 or blocking its signaling pathway significantly delayed the progression of bone lesions. Combination therapy using anti-LILRB4 and bortezomib has also shown promising results in inhibiting bone damage in multiple myeloma.

5 | LILRB4 IN OTHER DISEASES

LILRB4 has become increasingly recognized as a significant factor in the pathogenesis of various diseases. This section discusses the pivotal role of LILRB4 in different diseases and its potential as a therapeutic target.

5.1 | Immune system disorders

LILRB4 plays a notable role in the pathogenesis of systemic lupus erythematosus (SLE). Jensen et al. [61] revealed that functional polymorphisms in ILT3 correlate with increased pro-inflammatory cytokine levels in SLE patients, suggesting a link between ILT3 genetic variations and the disease's inflammatory aspects. Furthermore, blocking the interaction between LILRB4 and FN significantly ameliorates autoimmune manifestations in lupus-prone mice [15], indicating the therapeutic potential of targeting LILRB4 in SLE management.

The immunosuppressive capabilities of LILRB4 extend to allergic reactions. Bussmann et al. [62] and subsequent studies [63, 64] demonstrated that ILT3 and ILT4-mediated suppression effectively mitigate allergic responses. LILRB4's presence on dendritic cells and eosinophils is particularly crucial in dampening allergic inflammation, highlighting its role in modulating immune responses against allergens.

LILRB4 has emerged as a key factor in promoting allograft tolerance. Chang et al. [65], Vlad et al. [66], and others [67, 68] showed that allogeneic antigen-specific T suppressor cells in patients without rejection significantly upregulate ILT3 and ILT4 in antigen-presenting cells. This finding underscores LILRB4's potential role in enhancing transplant tolerance and reducing the likelihood of rejection.

The therapeutic promise of LILRB4-targeted interventions is further evidenced in multiple sclerosis. Xu et al. [69] demonstrated that administering ILT3.Fc decelerated disease progression in a mouse model of multiple sclerosis, shedding light on the potential application of ILT3.Fc-based treatments in this debilitating neurological disorder.

LILRB4's role in vitamin D deficiency-related immune disorders has been gaining attention. Rochat et al. [70] and Koivisto et al. [71] suggested a novel link between maternal vitamin D intake during pregnancy and the regulation of ILT3 and ILT4 mRNA levels in cord blood, potentially fostering early immune tolerance in the offspring. This discovery opens new research directions for understanding and potentially intervening in immune disorders associated with vitamin D deficiency.

5.2 | Infectious diseases

LILRB4 has significant implications in the immunological landscape of human immunodeficiency virus (HIV) infection. Vlad et al. [72] discovered that elevated serum interleukin (IL)-10 levels in HIV-positive individuals lead to the upregulation of ILT4 in monocytes. This finding indicates a potential mechanism through which HIV influences immune regulation and suggests that LILRB4 might play a role in disease progression or response to HIV therapy.

The role of LILRB4 extends to bacterial infections, impacting both maternal health and diagnostic processes. Li et al. [73, 74] and Zhao et al. [75] reported LILRB4's involvement in adverse pregnancy outcomes associated with Neisseria gonorrhoeae infection and its potential as a diagnostic biomarker for tuberculosis. These studies underscore the importance of LILRB4 in bacterial pathogenesis and maternal-fetal health. In parasitic infections, LILRB4 was shown to play a role in Toxoplasma gondii infection. Li et al. [76] reported that LILRB4 regulates the function of decidual myeloid-derived suppressor cells via the SHP-2/STAT6 pathway during T. gondii infection, indicating its potential impact on maternal-fetal immunity and the management of parasitic infections during pregnancy.

LILRB4's role in modulating immune responses is further exemplified in Salmonella infections. Brown et al. [77] reported that LILRB4 influences the phenotype of antigen-presenting cells during Salmonella infection, suggesting its involvement in the body's defense mechanism against this pathogen and potential implications for vaccine development or therapeutic strategies.

LILRB4 was also shown to function in coronavirus disease 2019 (COVID-19). Patel et al. [78] demonstrated that changes in LILRB4 levels correlate with the severity of COVID-19, proposing its use as an early biomarker and a potential therapeutic target.

5.3 | LILRB4 in other conditions

Recent research has highlighted the role of LILRB4 in Alzheimer's disease (AD). Microglia, which play a crucial role in limiting the progression of AD by constraining amyloid-β (Aβ) pathology, express high levels of LILRB4. In a mouse model of AD, systemic treatment with an anti-human LILRB4 monoclonal antibody (mAb) reduced Aβ load, mitigated some Aβ-related behavioral abnormalities, enhanced microglia activity, and attenuated expression of interferon-induced genes. These findings suggest that targeting LILRB4 could be a potential therapeutic strategy for AD by modulating microglial activity and reducing amyloid pathology [79].

Aortic dissection is a severe vascular disease with high mortality and morbidity rates. Recent studies have identified several differentially expressed genes in aortic dissection, including LILRB4 [80, 81]. Downregulation of LILRB4 promoted the contractile phenotypic switch and apoptosis of human aortic smooth muscle cells in an in

vitro model of aortic dissection. This downregulation also promoted extracellular matrix (ECM) stability by increasing the expression of contractile proteins α-SMA and SM22α, while decreasing the expression of ECM-degrading proteins such as MMP2 and CTGF [81]. Further investigations showed that LILRB4 knockdown in animal models not only reduced the incidence and severity of aortic dissection but also inhibited pyroptosis and the JAK2/STAT3 signaling pathway. The JAK2 inhibitor AG490 demonstrated additional benefits, including reduced cell viability and migration, enhanced apoptosis, and induced cell cycle arrest in PDGF-BB-stimulated HASMCs [80]. These findings suggest that LILRB4 may be a potential therapeutic target for aortic dissection, providing new approaches for clinical treatment by stabilizing the ECM and reducing inflammation and cell death.

LILRB4 also functions in the digestive system and plays a role in inflammatory bowel disease. Munitz et al.'s research [82] revealed the role of paired immunoglobulin-like type 2 receptor beta (PIR-B), a receptor similar to LILRB4, in modulating macrophage responses to pathogenic bacteria and chronic intestinal inflammation. This finding suggests that inhibitory receptors like PIR-B, and by extension LILRB4, could be potent therapeutic targets for managing inflammatory bowel disease. This highlights the potential of targeting immune checkpoint molecules in the treatment of inflammatory disorders of the digestive tract.

LILRB4 also plays a significant role in liver-related disorders, particularly nonalcoholic fatty liver disease (NAFLD). Lu et al. [83] proposed that enhancing the expression or activation of LILRB4 in the liver could be a promising therapeutic strategy for treating NAFLD and associated metabolic disorders. This approach could open new avenues for addressing the growing challenge of NAFLD, which is closely linked to metabolic syndrome and poses significant health risks.

LILRB4 plays a critical function in respiratory conditions, Qiu et al. [84] demonstrated that LILRB4 deficiency exacerbates acute lung injury through NF-κB signaling pathways in bone marrow-derived macrophages. This insight suggests that LILRB4 might serve as a protective factor in acute lung injury, highlighting its potential as a therapeutic target in acute respiratory disorders.

In chronic respiratory diseases like chronic obstructive pulmonary disease and emphysema, LILRB4 has a significant role. Mitsune et al. [85] showed that LILRB4 is upregulated in interstitial macrophages in chronic obstructive pulmonary disease patients, suggesting a protective role against emphysema formation. This finding indicates the importance of LILRB4 in modulating chronic inflammatory responses in the lungs.

The influence of LILRB4 extends to cardiac health, particularly in pathological cardiac hypertrophy. Li et al. [86] reported that LILRB4 negatively modulates pathological cardiac hypertrophy by activating NF-κB signaling pathways. This discovery opens potential research focuses for targeting LILRB4 in the management of cardiac hypertrophy and related cardiovascular conditions.

LILRB4's role in pediatric inflammatory conditions is highlighted in Kawasaki disease, also known as mucocutaneous lymph node syndrome. Sugahara-Tobinai et al. [87] found enhanced ILT3/LILRB4 expression in peripheral blood antibody-secreting cells during the acute phase of Kawasaki disease, suggesting a potential role for LILRB4 in the immune response associated with this disease.

LILRB4's involvement in general inflammatory responses is well-documented. Qiu et al. [84] and Brown et al. [77] showed that LILRB4 expression on monocyte-lineage cells, including macrophages, is upregulated under inflammatory stimuli. Moreover, Xu et al. [69] revealed that recombinant human ILT3.Fc protein binds mouse immune cells, effectively inhibiting the release of pro-inflammatory cytokines. These findings collectively suggest that LILRB4 plays a central role in modulating the body's inflammatory responses, with implications for a broad range of inflammatory conditions.

6 | THERAPEUTIC APPROACHES TARGETING LILRB4

The translation of basic research on LILRB4 into therapeutic biologics has marked a significant breakthrough in immunotherapy. Especially noteworthy are the advancements in the development of monoclonal antibodies and peptide inhibitors targeting LILRB4, which have opened new avenues for treating a variety of diseases, particularly in oncology.

6.1 | Monoclonal antibody development

One of the recent advancements in this field is the development of humanized mAbs targeting LILRB4. These antibodies offer a promising approach to counteracting the immunosuppressive effects of diseases like AML. Gui et al. [41] revealed the critical role of these antibodies in bridging the gap between understanding LILRB4's role and applying it in practical therapeutic applications. The exploration of LILRB4 as a therapeutic target highlights its potential to modulate immune responses and enhance treatment outcomes.

6.2 | Molecular dynamics and peptide inhibitors

Exploration of molecular interactions between LILRB4 and its mAb (h128-3) through molecular dynamics simulations has been a pivotal advancement. Chao et al. [88] used biomimetic design techniques to develop smaller peptide inhibitors akin to mAb h128-3. These peptide inhibitors are envisaged to provide more targeted and efficient inhibition of LILRB4. This innovative approach not only leverages a detailed molecular understanding of LILRB4 interactions but also offers a novel therapeutic strategy, potentially transforming the treatment landscape for diseases where LILRB4 plays a crucial role. A better understanding of the pathways and interactions involving LILRB4 will lead to the development of more effective therapeutic agents.

7 | CONCLUSION AND FUTURE DIRECTIONS

LILRB4 plays a critical role in immune regulation and has a significant impact on various diseases, especially cancer. LILRB4 functions as a key immune checkpoint, modulating responses by either activation or suppression and its interactions within the tumor microenvironment are crucial for tumor progression and immune evasion.

Research has demonstrated the involvement of LILRB4 in several cancers, including leukemia, pancreatic cancer, NSCLC, colorectal cancer, melanoma, and liver cancer. Multiple LILRB4 targeted therapies, such as mAbs and peptide inhibitors, are in development as therapeutic strategies for cancer treatment. Future research should focus on further elucidating LILRB4's mechanisms, with the aim of identifying more effective therapeutic agents and validating potential therapeutic strategies through clinical trials.

In summary, LILRB4 is a pivotal therapeutic target in cancer treatment. Its modulation offers promising strategies for enhancing immune responses against tumors, making it a cornerstone for future cancer therapies and precision medicine.

AUTHOR CONTRIBUTIONS

Qi Liu: Conceptualization (equal); investigation (lead); methodology (equal); visualization (lead); writing—original draft (equal). **Yuyang Liu**: Investigation (supporting); methodology (equal); visualization (supporting); writing—original draft (equal). **Zhanyu Yang**: Conceptualization (equal); investigation (supporting); methodology (equal); project administration (lead); supervision (lead); visualization (supporting); writing—review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Not applicable.

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