Targeting leukocyte immunoglobulin-like receptor B2 in the tumor microenvironment: A new treatment prospect for solid tumors (Review)

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Abstract. Leukocyte immunoglobulin-like receptor B2 (LILRB2) functions as an immunosuppressive receptor that has a prominent role in immune regulation. The expression of LILRB2 is higher in a variety of solid malignant tumors compared with that in corresponding normal tissues. LILRB2 can be expressed in tumor cells and tumor stromal cells within the tumor microenvironment. Upregulation of LILRB2 in tumors is significantly associated with a poorer tumor phenotype, increased tolerance to certain therapeutic drugs, tumor immune escape and shorter patient overall survival time. Therefore, LILRB2 can be utilized as a novel biomarker to predict the prognosis of patients with solid malignant tumors, and targeting LILRB2 may be an effective strategy for targeted cancer therapy. The present review provides a general overview of the role and mechanisms of LILRB2 in the microenvironment of solid tumors, and emphasizes the significance of targeting LILRB2 as a promising approach for tumor-specific therapy.

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Abbreviations: LILRB2, leukocyte immunoglobulin-like receptor B2; TME, tumor microenvironment; PirB, paired immunoglobulin-like receptor B; NK, natural killer; DCs, dendritic cells; ITIMs, immunoreceptor tyrosine-based switch motifs; SHP-1, tyrosine phosphatase-1; MHC, major histocompatibility complex; HLA, human leukocyte antigen; ANGPTLs, angiopoietin-like proteins; NSCLC, non-small cell lung cancer; Treg, regulatory T cells; CaMK1, calcium/calmodulin-dependent protein kinase 1; TAM, tumor-associated macrophage; CRC, colorectal cancer; LPS, lipopolysaccharide; PGE2, prostaglandin E2; COX, cyclooxygenase; IFN, interferon

Key words: LILRB2, tumor microenvironment, drugs, immune, therapy

Contents

1. Introduction

Leukocyte immunoglobulin-like receptor B2 (LILRB2), also known as Ig-like transcript (ILT)4 or CD85d, is an immunosuppressive receptor that is expressed in various types of cells (1,2). The homologue of LILRB2 in mice is known as paired immunoglobulin-like receptor B (PirB) (3). Under normal physiological conditions, LILRB2 is primarily expressed in monocytes and B cells, with lower expression in endothelial cells, natural killer (NK) cells, macrophages, placental cells and dendritic cells (DCs) (4). As a critical immune molecule, LILRB2 is closely associated with the activation and differentiation of immune cells, and plays an important role in innate and adaptive immunity (2). Furthermore, studies have demonstrated that LILRB2 has a significant influence on synaptic plasticity, neurite growth (5) and the proliferation of hematopoietic stem cells (6).

Structurally, LILRB2 is composed of four extracellular Ig-like domains, a transmembrane domain and a cytoplasmic portion containing three immunoreceptor tyrosine-based switch motifs (ITIMs). ITIMs can regulate cell signal transduction by recruiting the SH2-containing proteins, tyrosine phosphatase (SHP)-1 and SHP-2 (7). Overall, two types of LILRB2 ligands have been discovered to date. The first is the classical or non-classical major histocompatibility complex (MHC)-I molecule, which is referred to as human leukocyte antigen (HLA) in humans. HLA-G has been shown to exhibit the highest binding ability to LILRB2 among HLA molecules (8). The other type of LILRB2 ligand includes angiopoietin-like proteins (ANGPTLs), among which ANGPTL2 and ANGPTL5 demonstrate the highest binding ability (9).

Recently, accumulating evidence has suggested that LILRB2 promotes the occurrence and progression of

endometrial cancer, lung cancer, breast cancer, hepatocellular carcinoma, colorectal cancer, ovarian cancer, and clear cell renal cell carcinoma (7,10-17). Research on LILRB2 in tumors has indicated that LILRB2 can be found in tumor cells and stromal cells within the tumor microenvironment (TME) of certain malignant tumors. This enrichment can regulate the malignant behavior of tumor cells and promote their immune escape (18). Moreover, LILRB2 is also positively associated with immunosuppression, tumor cell proliferation, invasion and metastasis (11). Unconventionally high expression of LILRB2 has been observed in hematological malignant tumor cells such as B-cell chronic lymphocytic leukemia, T-cell lymphoma and acute monocytic leukemia. Increased LILRB2 levels are positively associated with disease progression (9). The role of LILRB2 in hematological tumors and related therapies has been adequately studied, but it is still in the development stage in solid tumors (9). Overall, the findings suggest that understanding the role of LILRB2 within the TME of solid tumors presents opportunities for therapeutic interventions aimed at inhibiting its effects on tumor progression. This suggests that targeting LILRB2 may offer a new approach for solid tumor targeted therapy.

2. Roles and functions of LILRB2 in solid tumors

LILRB2 and its involvement in human tumors. Clinical studies have revealed an association between upregulation of LILRB2 and a diverse number of tumors, such as endometrial cancer (10), colorectal cancer (CRC) (15), non-small cell lung cancer (NSCLC) (12), lung adenocarcinoma (13), hepatocellular carcinoma (14), breast cancer (7), renal cell carcinoma (17) and ovarian cancer (16).

LILRB2 expression has been detected on the tumor cell membrane, in the cytoplasm or both (7,15), and it is also present on the surface of $CD4^+$ and $CD8^+$ T cells in the TME (12). Increased LILRB2 expression level has been revealed to be associated with a worse patient prognosis. Bioinformatics analysis revealed that patients with malignant gliomas with high LILRB2 expression have a 5-year survival rate that is ~20% lower compared with that in patients with low LILRB2 expression (19). In renal clear cell carcinoma, the difference is ~10% (20). Furthermore, LILRB2 is upregulated in the early stages of esophageal cancer (21). Histopathological analysis demonstrates that higher levels of LILRB2 in breast cancer, CRC, lung adenocarcinoma and hepatocellular carcinoma tissues are significantly associated with larger primary tumors, poorer cell differentiation, lymph node metastasis, reduced T-cell infiltration, advanced disease stage and shorter overall patient survival time (7,13-15,22). The results indicate that LILRB2 may have early diagnostic or prognostic value in these tumors.

Additionally, analysis of T-cell subsets in patients with CRC or lung adenocarcinoma reveals that overexpression of LILRB2 is linked to decreased levels of $CD3^+$ and $CD8^+$ T cells, and increased levels of $FOXP3^+$ regulatory T (Treg) cells within the TME (13,22). These results indicate that LILRB2 can promote the tumor to display a more malignant phenotype and induce the formation of inhibitory immune microenvironment, thus promoting tumor progression. Therefore, LILRB2 may become a novel biomarker for predicting the prognosis of patients with solid tumors.

LILRB2 and experimental tumors. Experimental studies have confirmed an increase in LILRB2 expression levels in tumor cells compared with corresponding controls. Furthermore, there is evidence demonstrating that overexpression of LILRB2 is closely related to the malignancy of tumor cells or a more malignant immune microenvironment (1,2,10,13,18).

Cell line experiments have confirmed that inhibition of LILRB2 expression in endometrial cancer and NSCLC cells leads to a prominent reduction in cell proliferation, colony formation, migration and invasion (10,12). In addition, it leads to increased levels of apoptosis and cell cycle blockage at the G_0/G_1 phase (10,12,23,24). Shao *et al* (25) injected LILRB2-knockdown or control HC1A endometrial cancer cells into NOD-SCID mice (non-obese diabetic-severe combined immunodeficiency mice, which exhibit bone marrow dysfunction, characterized by deficiencies in T and B cells, and hypoactivity of NK cells) and revealed that tumor volume and weight in the LILRB2-knockdown group decreased by more than half compared with that in the control group. The blockade of LILRB2 has been shown to enhance the effect of T-cell immune checkpoint inhibitors, reduce the Treg infiltration in tumor tissue and polarize tumor-infiltrating myeloid cells toward an inflammatory phenotype in NSCLC tissues, ultimately promoting antitumor immunity (26). Consistent with this study, LILRB2 overexpression promotes immune tolerance among DCs, resulting in an inefficient T-cell response for patients with hepatocellular carcinoma, and suppresses tumor immunity by recruiting M2-type tumor-associated macrophages (TAMs) and impairing T-cell proliferation and function (27).

These findings reveal that LILRB2 plays an important role in maintaining the malignant phenotype of tumor cells while suppressing tumor immunity. Therefore, the knockdown of LILRB2 may be an efficient strategy for targeted therapy against solid tumors.

3. Mechanisms of LILRB2 in tumor progression

Studies have demonstrated the overexpression or inducibility of LILRB2 in solid tumors (2,7,10,13,14), highlighting its involvement in promoting tumor proliferation and growth, and invasion and metastasis, as well as maintaining an immunosuppressive microenvironment through various mechanisms.

Mechanisms of tumor cell-derived LILRB2. LILRB2 is highly expressed in diverse types of tumor cells, contributing to their malignancy (2).

In NSCLC, LILRB2 modulates the proliferation of NSCLC A549 cells via the SHP-2/calcium/calmodulin-dependent protein kinase 1 (CaMK1)/cAMP response element-binding protein (CREB) axis (12). In LILRB2-deficient A549 cells, the phosphorylation of SHP-2 is significantly decreased, leading to decreased activation of CaMK1 and reduced levels of phosphorylated-CREB, a target of CaMK1 (12). As a transcription factor, the activity of CREB can be significantly increased by phosphorylation, promoting the expression of genes linked to

proliferation and migration, thereby promoting the malignant transformation of tumor cells (28). Therefore, LILRB2 deficiency can reduce the proliferation of A549 cells through this pathway. This signaling axis also facilitates the proliferation and migration of endometrial cancer Ishikawa and HEC-1A cells (25). LILRB2 can also promote the invasion and migration of NSCLC cells by upregulating MMP-2 expression (29), whose function is to degrade the extracellular matrix (30). Additionally, by interacting with HLA-G, LILRB2 can enhance ERK1/2 phosphorylation and upregulate VEGF-C, thereby promoting NSCLC progression by activating the classical ERK pathway and increasing angiogenesis (23,31). Moreover, LILRB2 overexpression triggered by EGFR activation increases the recruitment of TAMs and their polarization towards an M2-like phenotype, which further promotes the T-cell dysfunction induced by TAMs in NSCLC (32).

In CRC, LILRB2 promotes the proliferation, invasion and migration of CRC HT29 and SW480 cells, while enhancing the expression of HLA-G, one of its ligands. Furthermore, the HLA-G fusion protein notably increases the expression of LILRB2 in a dose-dependent manner. This interaction facilitates the progression of CRC HT29 cells by activating the AKT and ERK signaling pathways (24). Additionally, a study using a mouse model showed that when CRC MC-38 cells overexpressing PirB (the mouse homologue of LILRB2) are injected into mice, it induces Treg infiltration and reduces production of interferon (IFN)-γ in tumor-infiltrating lymphocytes compared to mice injected with control cell (22).

In pancreatic ductal carcinoma, the autocrine signaling between LILRB2 and ANGPTL2 plays an important role in sustaining cell metastasis during epithelial-mesenchymal transition and in early pancreatic cancer precursors. Blocking LILRB2 reduces ANGPTL2-induced cell proliferation and invasion. Serial KRAS activation, HER2 expression and p16/p14-silencing are sufficient to enhance ANGPTL2 secretion and LILRB2 expression (33).

Additionally, Gao *et al* (18) revealed that LILRB2/PirB from NSCLC, prostate cancer and breast cancer cells can enhance fatty acid synthesis and lipid accumulation in these cells by activating the ERK1/2 signaling pathway through research on human cells and breast cancer and melanoma mouse tumor models. By contrast, in the tumor cell lines A549, H1299, ZR751, M628 and PC-3, LILRB2 knockdown notably decreases the expression of two limiting enzymes, acetyl-CoA carboxylases 1 and fatty acid synthase, thus inhibiting fatty acid synthesis and lipid accumulation. Therefore, high levels of LILRB2 in tumors can lead to fatty acid and lipid accumulation that ultimately leads to effector T-cell senescence and tumor progression (18).

In summary, tumor cell-derived LILRB2 can promote cancer malignancy by activating classical or non-classical pathways by itself or by interacting with its ligands, promoting angiogenesis and EMT, reducing the secretion of tumor-killing factors, and promoting the accumulation of fatty acids and lipids. The main mechanisms of action of tumor cell-derived LILRB2 are summarized in Fig. 1.

Mechanisms of immune cell-derived LILRB2. LILRB2 is expressed in various immune cells and is involved in regulating their state and function.

Macrophages are phagocytic cells that perform a pivotal role in eliminating foreign particles, aging or damaged cells, killing tumor cells and participating in the immune response (34). Macrophages can be classified as M1 (pro-inflammatory) and M2 (anti-inflammatory) types, which are associated with NF-κB/STAT1 or STAT6 activation, respectively (35). In the presence of macrophage-stimulating factor lipopolysaccharide (LPS) or IFN-γ, the LILRB2 antagonism causes macrophages to produce an inflammatory phenotype, and increase the phosphorylation of NF-κB, ERK1/2, p38 and STAT1 (just in response to IFN-γ); the reason for these changes is the interruption of SHP-1 activation signal and the inhibition of the PI3K/AKT pathway caused by LILRB2 blockade (26). Additionally, antagonizing LILRB2 increases macrophage resistance to IL-4-mediated humoral cytokine-dependent activation of STAT6, thereby alleviating macrophage inhibition of T-cell proliferation (26).

DCs are important in both innate and acquired immunity due to their ability to uptake and present antigens (36); their functions can be modulated by inhibitory receptors, including LILRB2, which is linked to the tolerogenic phenotype of DCs (37,38). HLA-G inhibits the maturation and differentiation of LILRB2-positive DCs by recruiting SHP-1 and SHP-2, resulting in increased IL-6 expression and STAT3 activation (39). In addition, IFN-γ, TNF-α and IL-10 can induce LILRB2 expression upregulation in DCs, promoting a pro-tolerogenic state of DCs (37,40,41). Furthermore, the presence of LILRB2 on DC surfaces can influence T cells through various pathways. Tryptophan deprivation induces tolerogenic DCs expressing a high level of LILRB2 and LILRB4 through a GCN2-mediated stress response pathway, which induces the production of $CD4^+CD25^+$ Tregs (42). A subset of DCs with high expression of LILRB2 and HLA-G can secrete abundant IL-10 and induce adaptive type 1 Treg cells through IL-10-related pathways (43).

In mouse models, PirB has been detected in T-cell progenitors, but rarely in mature T cells; and after antigen or allogeneic stimulation, PirB combined with MHC-I inhibits proximal T-cell receptor signaling, leading to reduced T-helper type 1 response in peripheral T cells that ectopically express PirB (44). Thus, PirB regulates the development of early T lymphocytes.

In summary, LILRB2 mainly affects macrophages and DCs. Low LILRB2 levels can promote the function of the immune system, whereas high LILRB2 levels have the opposite effect.

4. Impact of LILRB2 on drug response

Recent research indicates that LILRB2 can enhance the tolerance of cells in the TME to certain drugs, potentially leading to the reduced efficacy of tumor drug therapy.

Cyclosporine A. Cyclosporine A is a classical non-cytotoxic immunosuppressant that is involved in the treatment of inflammation and autoimmune diseases (45). Cyclosporine A has also shown potential for prostate cancer and renal cell carcinoma treatment, particularly in reversing multidrug resistance in tumors and enhancing the therapeutic effect of chemotherapy drugs (46,47).

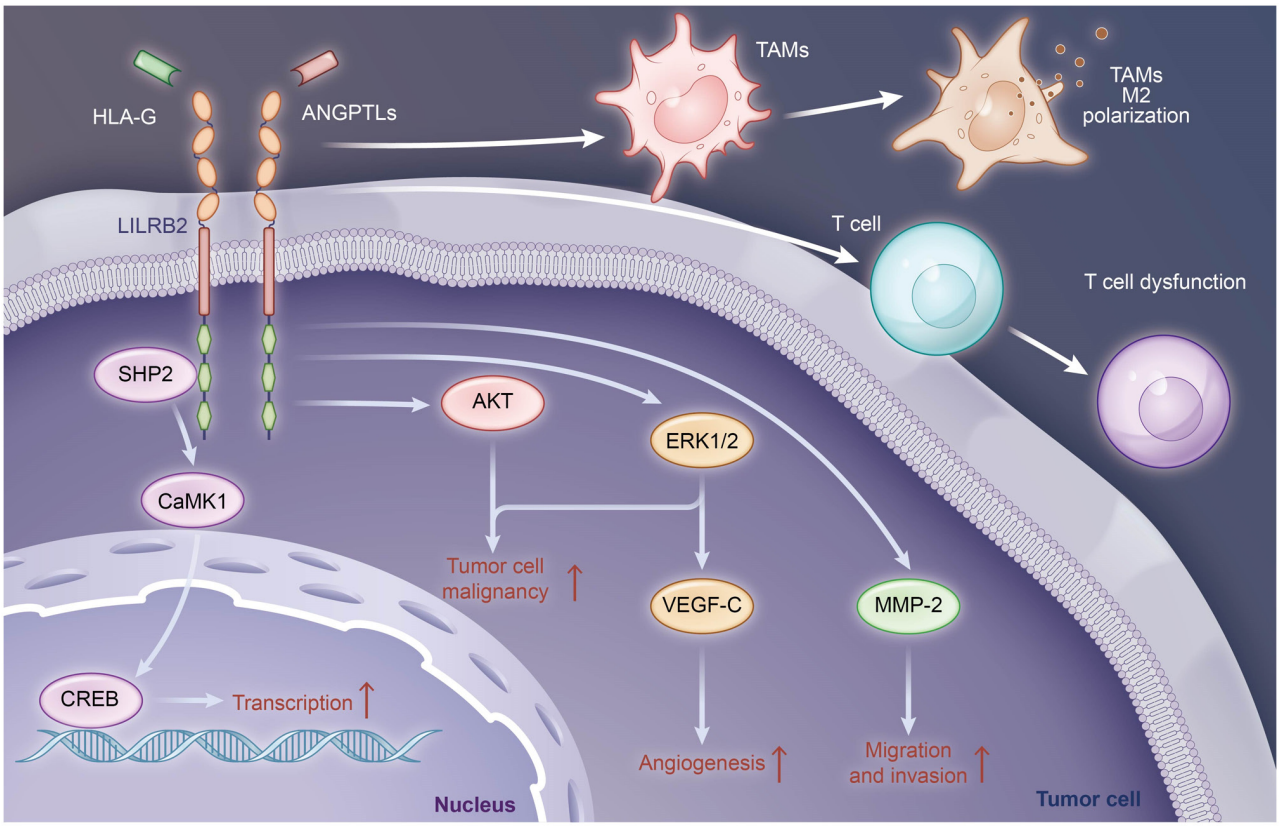

Figure 1. Tumor cell-derived LILRB2 binds to ligands HLA-G or ANGPTLs and activates downstream signaling pathways related to tumor progression, as well as promotes the M2 polarization of TAMs and induces the dysfunction of T cells. LILRB2, leukocyte immunoglobulin-like receptor B2; SHP-2, tyrosine phosphatase-2; ANGPTLs, angiopoietin-like proteins; CaMK1, calcium/calmodulin-dependent protein kinase 1; TAMs, tumor-associated macrophages; CREB, cAMP response element-binding protein; HLA, human leukocyte antigen.

Si *et al* (48) exposed NK cells to different doses of cyclosporine A and observed a significant increase in LILRB2 expression on the NK cells in a dose- and time-dependent manner. After treatment with cyclosporine A, the proliferation of NK cells decreased and the cytotoxic activity of NK cells against the human gastric cancer BGC-823 cell line and choriocarcinoma JEG-3 cell line was reduced. The results suggest that cyclosporine A upregulates LILRB2 expression on NK cells, thereby resulting in the inhibition of the anti-tumor activity of NK cells. Patients receiving cyclosporine A treatment for a long time may have decreased NK cell activity due to the upregulation of LILRB2, and thus decreased immune function (48). These findings highlight that LILRB2 overexpression in NK cells impairs the facilitating effect that cyclosporine A exerts on the anti-tumor immune response. Inhibition of LILRB2 expression may be an effective method to enhance the activity of NK cells and thus the function of the immune system.

Resveratrol. Resveratrol (3,4',5-trihydroxy-trans-stilbene) is an inartificial polyphenolic compound that is widely found in plants; it possesses various pharmacological properties, such as protection against cardiovascular ischemic injury, regulation of lipid metabolism, and anti-inflammatory and antitumor effects (49). Resveratrol has been demonstrated to inhibit tumor development and progression, and shows promising efficacy in the clinical treatment of colorectal and prostate cancer (50,51).

Resveratrol can induce DC tolerance, particularly during differentiation. In a previous study, costimulatory molecules CD40/80/86 and MHC-II were downregulated in tolerogenic DCs, while LILRB2 and ILT3 were induced. LILRB2 in DCs was not upregulated after treatment with resveratrol on day 5 prior to stimulation. However, when resveratrol was present during the whole process of DC differentiation, LILRB2 was significantly upregulated. Furthermore, DCs treated with resveratrol did not produce the antitumor factor IL-12p70 but instead produced more immunosuppressive factor IL-10. Thus, LILRB2 may act as a vital influencing factor in the tolerance of DCs induced by resveratrol and thereby affect the impact of DCs on tumors (52).

Niflumic acid. Niflumic acid is a commonly used non-steroidal anti-inflammatory drug, primarily functioning by inhibiting the activity of cyclooxygenase 2 (COX-2), and is predominantly prescribed for the treatment of rheumatoid arthritis and to alleviate inflammatory pain (53,54). Additionally, niflumic acid has demonstrated antitumor effects by promoting apoptosis in breast cancer, colon cancer and liver cancer cells and complexes of niflumic acid with metals such as Ni(II) and Co(II) showed better anti-tumor effects (55,56).

Svajger *et al* (57) revealed that niflumic acid can upregulate LILRB2 expression in LPS-induced mature monocyte-derived DCs. LILRB2 expression level was positively related to the concentration of niflumic acid administered, and negatively related to expression level of co-stimulatory molecules

CD80/86, indicating that LILRB2 influences LPS-induced tolerance in mature DCs treated with niflumic acid, which may impact their effectiveness against tumors.

Prostaglandin E2 (PGE2). PGE2 is a small molecule derived from arachidonic acid, and its synthesis is catalyzed by COX-1, COX-2 and PGE synthetase. PGE2 is widely distributed in animals and plays a role in the expansion and contraction of blood vessels, the control of blood pressure, the regulation of inflammation, and other physiological activities (58). However, in tumors, PGE2 is expressed at a high level (59).

The expression of LILRB2 significantly increases after the addition of PGE2 to monocytic-myeloid-derived suppressor cells (M-MDSCs) induced by granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6; and after blocking LILRB2, M-MDSCs induced by GM-CSF/IL-6 stimulate a low percentage of type 1 Treg cells (60). PGE2 promotes tumorigenesis by increasing the expression of LILRB2, which further promotes the development of M-MDSC-induced type 1 Treg cells, adversely affecting antitumor immunity (60). Therefore, targeting LILRB2 can reduce the tumor-promoting effect of PGE2.

IFNs. IFNs are a group of active proteins primarily produced by monocytes and lymphocytes, with a variety of functions, including antiviral activity, inhibition of cell proliferation, regulation of immunity and antitumor effects. IFNs can be mainly categorized into IFN-α, IFN-β and IFN-γ, among which IFN-α and IFN-γ play pivotal roles in antitumor immunity (61). Clinical application of IFN in tumor treatment has shown efficacy in inhibiting tumor growth, and its combination with other therapies can also improve antitumor treatment outcomes (62).

LILRB2 is notable in the induction and maintenance of tolerogenic DCs. The expression level of LILRB2 on immature DCs is significantly upregulated after treatment with IFN-α (1,000 U/ml) or high doses of IFN-γ (>500 U/ml), while the high level of LILRB2 is a universal feature of tolerogenic DCs (37,41). Furthermore, tolerogenic DCs can lead to tumor progression and are associated with poor patient outcomes (63). In addition, the stimulatory activity of DCs treated with IL-10 and IFN-α is low (37). Accordingly, LILRB2 may adversely affect the efficacy of IFN in tumor treatment.

In summary, the aforementioned drugs have been indicated to cause upregulated expression of LILRB2 on immune cells (mainly DCs, NK cells and M-MDSCs) within the TME, which is not conducive to the antitumor function of the immune system. Therefore, therapies targeting LILRB2 may improve the efficacy of these drugs.

5. Impact of LILRB2 on radiotherapy

Radiation therapy, which destroys the chromosomes of cells through radiation, is one of the common therapies for tumors (64). However, for a variety of reasons, tumors develop resistance to radiation therapy, resulting in treatment failure (65).

It has been demonstrated that LILRB2 can resist the effect of radiotherapy. In patients with lung adenocarcinoma, bioinformatics analysis has revealed that stereotactic body radiotherapy upregulates the expression of LILRB2 in tumor-infiltrating lymphocytes (66). Analogously, in patients with NSCLC, radiotherapy promotes LILRB2 expression, which increases M2-TAM migration by activating the NF-κB pathway and the secretion of chemokine CXCL1 (67). Radiation enhances LILRB2 expression in several NSCLC cell lines in a time-dependent manner, and knockdown of LILRB2 promotes the radiosensitivity of NSCLC cells (68). In addition, radiation can also facilitate NSCLC cellular senescence and the senescence-associated secretory phenotype, whereas blocking LILRB2 expression decreases these effects by suppressing the JAK2/STAT3 pathway (68). Thus, targeting LILRB2 can enhance tumor radiosensitivity.

6. Novel drugs targeting LILRB2

Currently, antibody drugs targeting LILRB2 have been developed and are being tested in clinical trials. Therapies involving LILRB2 antibody drugs primarily focus on enhancing the activity of immune cells in the TME, ultimately promoting T cell-mediated killing of tumors. These drugs have demonstrated prospective therapeutic effects when utilized alone or in combination with other treatments.

JTX-8064. JTX-8064 is a humanized monoclonal antibody that specifically targets LILRB2 and acts as an antagonist by inhibiting the interaction between LILRB2 and MHC-I (69,70).

An *in vitro* human tumor culture model obtained from lung, kidney and head and neck cancer revealed that the pharmacodynamic response induced by JTX-8064 was significantly higher compared with that of the isotype control (71). This is due to the transformation of human macrophages and DCs to immunostimulated inflammatory phenotypes after stimulation with JTX-8064, resulting in increased antigen presentation and enhanced T-cell activation (69-72). Furthermore, JTX-8064 can also improve the effectiveness of programmed cell death protein 1 (PD-1) inhibitors in treating tumors. The combination of JTX-8064 and anti-PD-1 can approximately double the expression level of IFN-γ obtained with treatment with anti-PD-1 alone (69).

Overall, these results provide evidence for the efficacy of targeting LILRB2 as a single drug or as an adjunct approach to cancer treatment.

MK-4830. MK-4830 is an IgG4 monoclonal antibody that binds to myeloid-specific LILRB2, whose functions include mitigating myelosuppression, facilitating TAMs reprogramming and increasing T cell function (73).

MK-4830 has been evaluated in a clinical trial (NCT03564691) as a monotherapy or in combination with pembrolizumab for the treatment of advanced melanoma, NSCLC, colorectal cancer and renal cell carcinoma. Relevant studies have revealed that MK-4830 demonstrates favorable tolerability, safety and antitumor activities in the treatment of advanced tumors, and its target binding ability is dose-dependent (73-75). Of 84 patients, 50 received MK4830 monotherapy, 34 received MK4830 combined with pembrolizumab, preliminary efficacy data show 11 objective responses. Among these, one of the patients received MK-4830

monotherapy and 5 patients did not respond to anti-PD-L1 therapy but improved with the combination of MK-4830. In addition, some patients experienced fatigue, nausea, decreased appetite or diarrhea during treatment (73). Patients who received MK-4830 and pembrolizumab simultaneously demonstrated a higher sensitivity to T-cell inflammation than expected compared with the response to pembrolizumab monotherapy (74).

These studies provide evidence for the potential value of MK-4830 as a novel immunotherapy or adjuvant therapeutic agent for tumors.

7. Conclusion

LILRB2 shows an increased expression level in the microenvironment of diverse solid tumors, promoting proliferation, colony formation, and the migration and invasion of tumor cells, and shifting the TME in an inhibitory direction, thereby facilitating tumorigenesis and progression. Consequently, LILRB2 may represent a novel target for tumor-targeted therapy. Researchers have developed new drugs, JTX-8064 and MK-4830, to target LILRB2, which have exhibited positive results in clinical trials either as monotherapy or in combination with other drugs. Further research may reveal that targeting LILRB2 constitutes a more effective strategy for targeted therapy of solid tumors in future.

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Authors' contributions

MC wrote the manuscript. JL and HL collected the literature, designed the figure and edited the manuscript. CZ and ZZ reviewed and revised the manuscript. NG drafted the manuscript and offered writing guidance. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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