

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

MENG CAO, JING LUAN, CUI ZHAI, HUAN LIU, ZHENHAO ZHANG and NA GUO

Institute of Basic and Translational Medicine, Xi'an Medical University, Xi'an, Shaanxi 710021, P.R. China

Received September 13, 2024; Accepted January 21, 2025

DOI: 10.3892/ol.2025.14927

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.

Contents

1. Introduction
2. Roles and functions of LILRB2 in solid tumors
3. Mechanisms of LILRB2 in tumor progression
4. Impact of LILRB2 on drug response
5. Impact of LILRB2 on radiotherapy
6. Novel drugs targeting LILRB2
7. Conclusion

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

Correspondence to: Professor Na Guo, Institute of Basic and Translational Medicine, Xi'an Medical University, 1 Xinwang Road, Weiyang, Xi'an, Shaanxi 710021, P.R. China
E-mail: guona@xjmu.edu.cn

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

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 G₀/G₁ 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- κ B/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- κ B, 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).

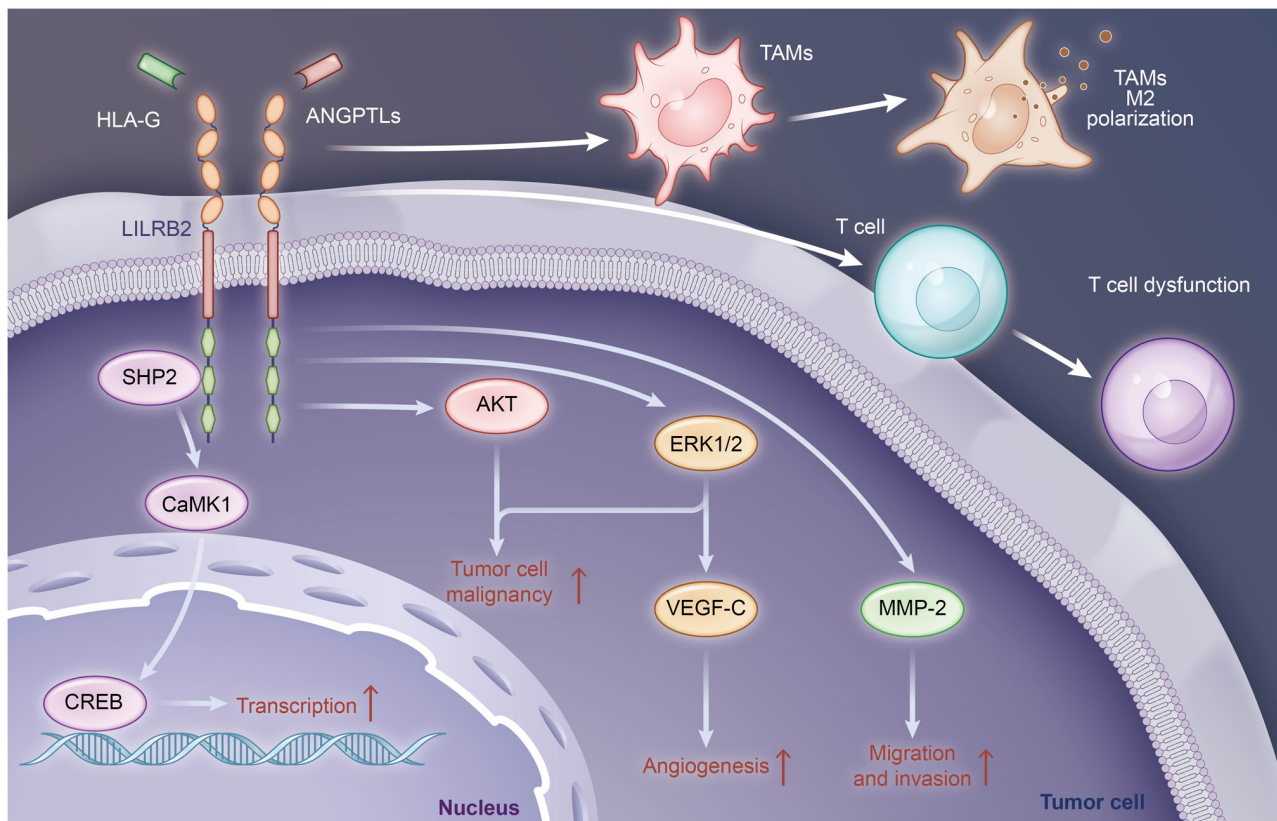


Figure 1. Tumor cell-derived LILRB2 binds to ligands HLA-G or ANGPTLs and activates downstream signaling pathways related to tumor progression, as well as promotes the M2 polarization of TAMs and induces the dysfunction of T cells. LILRB2, leukocyte immunoglobulin-like receptor B2; SHP-2, tyrosine phosphatase-2; 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 artificial 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- κ B 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.

Acknowledgements

Not applicable..

Funding

This study was funded by the National Natural Science Foundation of China (grant no. 82203692), the Natural Science Basic Research Program of Shaanxi Province (grant nos. 2021JQ-777 and 2023-JC-QN-0863), the Scientific Research Plan of Shaanxi Provincial Education Department (grant no. 21JS040), the Young Talent Fund of Association for Science and Technology in Shaanxi (grant no. 20220610) and the Innovation Team of Xi'an Medical University (grant no. 2021TD05 and 2021TD-48).

Availability of data and materials

Not applicable.

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.

References

1. Zhang P, Yu S, Li H, Liu C, Li J, Lin W, Gao A, Wang L, Gao W and Sun Y: ILT4 drives B7-H3 expression via PI3K/AKT/mTOR signalling and ILT4/B7-H3 co-expression correlates with poor prognosis in non-small cell lung cancer. *FEBS Lett* 589: 2248-2256, 2015.
2. Gao A, Sun Y and Peng G: ILT4 functions as a potential checkpoint molecule for tumor immunotherapy. *Biochim Biophys Acta Rev Cancer* 1869: 278-285, 2018.
3. Yue J, Zhang C, Shi X, Wei Y, Liu L, Liu S and Yang H: Activation of leukocyte immunoglobulin-like receptor B2 signaling pathway in cortical lesions of pediatric patients with focal cortical dysplasia type IIb and tuberous sclerosis complex. *Brain Dev* 41: 829-838, 2019.
4. Borges L and Cosman D: LIRs/ILTs/MIRs, inhibitory and stimulatory Ig-superfamily receptors expressed in myeloid and lymphoid cells. *Cytokine Growth Factor Rev* 11: 209-217, 2000.
5. Yue J, Li W, Liang C, Chen B, Chen X, Wang L, Zang Z, Yu S, Liu S, Li S and Yang H: Activation of LILRB2 signal pathway in temporal lobe epilepsy patients and in a pilocarpine induced epilepsy model. *Exp Neurol* 285: 51-60, 2016.
6. Deng M, Lu Z, Zheng J, Wan X, Chen X, Hirayasu K, Sun H, Lam Y, Chen L, Wang Q, *et al*: A motif in LILRB2 critical for Angptl2 binding and activation. *Blood* 124: 924-935, 2014.
7. Liu J, Wang L, Gao W, Li L, Cui X, Yang H, Lin W, Dang Q, Zhang N and Sun Y: Inhibitory receptor immunoglobulin-like transcript 4 was highly expressed in primary ductal and lobular breast cancer and significantly correlated with IL-10. *Diagn Pathol* 9: 85, 2014.
8. Carosella ED, Gregori S and Tronik-Le Roux D: HLA-G/LILRBs: A cancer immunotherapy challenge. *Trends Cancer* 7: 389-392, 2021.
9. Zheng J, Umikawa M, Cui C, Li J, Chen X, Zhang C, Huynh H, Kang X, Silvany R, Wan X, *et al*: Inhibitory receptors bind ANGPTLs and support blood stem cells and leukaemia development. *Nature* 485: 656-660, 2012.
10. Shao H, Ma L, Jin F, Zhou Y, Tao M and Teng Y: Immune inhibitory receptor LILRB2 is critical for the endometrial cancer progression. *Biochem Biophys Res Commun* 506: 243-250, 2018.
11. Sun Y, Liu J, Gao P, Wang Y and Liu C: Expression of Ig-like transcript 4 inhibitory receptor in human non-small cell lung cancer. *Chest* 134: 783-788, 2008.
12. Liu X, Yu X, Xie J, Zhan M, Yu Z, Xie L, Zeng H, Zhang F, Chen G, Yi X and Zheng J: ANGPTL2/LILRB2 signaling promotes the propagation of lung cancer cells. *Oncotarget* 6: 21004-21015, 2015.
13. Li Q, Li J, Wang S, Wang J, Chen X, Zhou D, Fang Y, Gao A and Sun Y: Overexpressed immunoglobulin-like transcript (ILT) 4 in lung adenocarcinoma is correlated with immunosuppressive T cell subset infiltration and poor patient outcomes. *Biomark Res* 8: 11, 2020.
14. Li X, Wei X, Xu H, Sha Z, Gao A, Sun Y, Li J and Xu L: Expression of leukocyte immunoglobulin-like receptor B2 in hepatocellular carcinoma and its clinical significance. *J Cancer Res Ther* 14: 1655-1659, 2018.
15. He J, Xu J, Yu X, Zhu H, Zeng Y, Fan D and Yi X: Overexpression of ANGPTL2 and LILRB2 as predictive and therapeutic biomarkers for metastasis and prognosis in colorectal cancer. *Int J Clin Exp Pathol* 11: 2281-2294, 2018.
16. Kun L, Yunyan P, Xiangshan Y, Hongxin N and Junyuan Y: Relationship between HPV 16/18 infection in ovarian cancer patients and expression of ILT4. *Chin J Nosocomiol* 24: 3901-3903, 2014.
17. García M, Palma MB, Verine J, Miriuka S, Inda AM, Errecalde AL, Desgrandchamps F, Carosella ED and Tronik-Le Roux D: The immune-checkpoint HLA-G/ILT4 is involved in the regulation of VEGF expression in clear cell renal cell carcinoma. *BMC Cancer* 20: 624, 2020.

18. Gao A, Liu X, Lin W, Wang J, Wang S, Si F, Huang L, Zhao Y, Sun Y and Peng G: Tumor-derived ILT4 induces T cell senescence and suppresses tumor immunity. *J Immunother Cancer* 9: e001536, 2021.
19. Li Y, Deng G, Qi Y, Zhang H, Gao L, Jiang H, Ye Z, Liu B and Chen Q: Bioinformatic profiling of Prognosis-related genes in malignant glioma microenvironment. *Med Sci Monit* 26: e924054, 2020.
20. Chalbatani GM, Momeni SA, Mohammadi Hadloo MH, Karimi Z, Hadizadeh M, Jalali SA, Miri SR, Memari F and Hamblin MR: Comprehensive analysis of ceRNA networks to determine genes related to prognosis, overall survival, and immune infiltration in clear cell renal carcinoma. *Comput Biol Med* 141: 105043, 2022.
21. Warnecke-Eberz U, Metzger R, Hölscher AH, Drebber U and Bollschweiler E: Diagnostic marker signature for esophageal cancer from transcriptome analysis. *Tumour Biol* 37: 6349-6358, 2016.
22. Yang Z, Gao A, Shi W, Wang J, Zhang X, Xu Z, Xu T, Zheng Y, Sun Y and Yang F: ILT4 in colorectal cancer cells induces suppressive T cell contexture and disease progression. *Oncotargets Ther* 14: 4239-4254, 2021.
23. Zhang P, Guo X, Li J, Yu S, Wang L, Jiang G, Yang D, Wei Z, Zhang N, Liu J and Sun Y: Immunoglobulin-like transcript 4 promotes tumor progression and metastasis and up-regulates VEGF-C expression via ERK signaling pathway in non-small cell lung cancer. *Oncotarget* 6: 13550-13563, 2015.
24. Cai Z, Wang L, Han Y, Gao W, Wei X, Gong R, Zhu M, Sun Y and Yu S: Immunoglobulin-like transcript 4 and human leukocyte antigen-G interaction promotes the progression of human colorectal cancer. *Int J Oncol* 54: 1943-1954, 2019.
25. Shao H, Ma L, Jin F, Zhou Y, Tao M and Teng Y: Immune inhibitory receptor LILRB2 is critical for the endometrial cancer progression. *Biochem Biophys Res Commun* 506: 243-250, 2018.
26. Chen HM, van der Touw W, Wang YS, Kang K, Mai S, Zhang J, Alsina-Beauchamp D, Duty JA, Mungamuri SK, Zhang B, *et al*: Blocking immunoinhibitory receptor LILRB2 reprograms tumor-associated myeloid cells and promotes antitumor immunity. *J Clin Invest* 128: 5647-5662, 2018.
27. Fan J, Han J, Li J, Gu A, Yin D, Song F, Wang L and Yi Y: The expression and function of immunoglobulin-like transcript 4 in dendritic cells from patients with hepatocellular carcinoma. *Hum Immunol* 81: 714-725, 2020.
28. Cho EC, Mitton B and Sakamoto KM: CREB and leukemogenesis. *Crit Rev Oncog* 16: 37-46, 2011.
29. Liu JF, Li J, Yan P, Gong WJ and Sun YP: Silencing of ILT4 suppresses migration and invasion of non-small cell lung cancer cells by inhibiting MMP-2. *Int J Clin Exp Med* 12: 5306-5314, 2019.
30. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, Ramirez-Acuña JM, Perez-Romero BA, Guerrero-Rodriguez JF, Martinez-Avila N and Martinez-Fierro ML: The roles of matrix metalloproteinases and their inhibitors in human diseases. *Int J Mol Sci* 21: 9739, 2020.
31. Zhang Y, Zhao J, Qiu L, Zhang P, Li J, Yang D, Wei X, Han Y, Nie S and Sun Y: Co-expression of ILT4/HLA-G in human non-small cell lung cancer correlates with poor prognosis and ILT4-HLA-G interaction activates ERK signaling. *Tumour Biol* 37: 11187-11198, 2016.
32. Chen X, Gao A, Zhang F, Yang Z, Wang S, Fang Y, Li J, Wang J, Shi W, Wang L, *et al*: ILT4 inhibition prevents TAM- and dysfunctional T cell-mediated immunosuppression and enhances the efficacy of anti-PD-L1 therapy in NSCLC with EGFR activation. *Theranostics* 11: 3392-3416, 2021.
33. Carbone C, Piro G, Fassan M, Tamburrino A, Mina MM, Zanotto M, Chiao PJ, Bassi C, Scarpa A, Tortora G and Melisi D: An angiopoietin-like protein 2 autocrine signaling promotes EMT during pancreatic ductal carcinogenesis. *Oncotarget* 6: 13822-13834, 2015.
34. Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, Seifi B, Mohammadi A, Afshari JT and Sahebkar A: Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol* 233: 6425-6440, 2018.
35. Martinez FO and Gordon S: The M1 and M2 paradigm of macrophage activation: Time for reassessment. *F1000Prime Rep* 6: 13, 2014.
36. Gardner A, de Mingo Pulido Á and Ruffell B: Dendritic cells and their role in immunotherapy. *Front Immunol* 11: 924, 2020.
37. Manavalan JS, Rossi PC, Vlad G, Piazza F, Yarinina A, Cortesini R, Mancini D and Suciu-Foca N: High expression of ILT3 and ILT4 is a general feature of tolerogenic dendritic cells. *Transpl Immunol* 11: 245-258, 2003.
38. Guerra-de Blas Pdel C, Villaseñor-Talavera YS, Cruz-González Dde J, Baranda L, Doníz-Padilla L, Abud-Mendoza C, González-Amaro R and Monsiváis-Urenda AE: Analysis of the expression and function of Immunoglobulin-like transcript 4 (ILT4, LILRB2) in dendritic cells from patients with systemic lupus erythematosus. *J Immunol Res* 2016: 4163094, 2016.
39. Liang S, Ristich V, Arase H, Dausset J, Carosella ED and Horuzsko A: Modulation of dendritic cell differentiation by HLA-G and ILT4 requires the IL-6-STAT3 signaling pathway. *Proc Natl Acad Sci USA* 105: 8357-8362, 2008.
40. Trojandt S, Bellinghausen I, Reske-Kunz AB and Bros M: Tumor-derived immuno-modulators induce overlapping pro-tolerogenic gene expression signatures in human dendritic cells. *Hum Immunol* 77: 1223-1231, 2016.
41. Svajger U, Obermajer N and Jeras M: IFN- γ -rich environment programs dendritic cells toward silencing of cytotoxic immune responses. *J Leukoc Biol* 95: 33-46, 2014.
42. Brenk M, Scheler M, Koch S, Neumann J, Takikawa O, Häcker G, Bieber T and von Bubnoff D: Tryptophan deprivation induces inhibitory receptors ILT3 and ILT4 on dendritic cells favoring the induction of human CD4⁺CD25⁺ Foxp3⁺ T regulatory cells. *J Immunol* 183: 145-154, 2009.
43. Gregori S, Magnani CF and Roncarolo MG: Role of human leukocyte antigen-G in the induction of adaptive type 1 regulatory T cells. *Hum Immunol* 70: 966-969, 2009.
44. Imada M, Masuda K, Satoh R, Ito Y, Goto Y, Matsuoka T, Endo S, Nakamura A, Kawamoto H and Takai T: Ectopically expressed PIR-B on T cells constitutively binds to MHC class I and attenuates T helper type 1 responses. *Int Immunol* 21: 1151-1161, 2009.
45. Patocka J, Nepovimova E, Kuca K and Wu W: Cyclosporine A: Chemistry and Toxicity-A review. *Curr Med Chem* 28: 3925-3934, 2021.
46. Qadir M, O'Loughlin KL, Fricke SM, Williamson NA, Greco WR, Minderman H and Baer MR: Cyclosporin A is a broad-spectrum multidrug resistance modulator. *Clin Cancer Res* 11: 2320-2326, 2005.
47. Liu Z, Jiang L, Li Y, Xie B, Xie J, Wang Z, Zhou X, Jiang H, Fang Y, Pan H and Han W: Cyclosporine A sensitizes lung cancer cells to crizotinib through inhibition of the Ca²⁺/calcineurin/Erk pathway. *EBioMedicine* 42: 326-339, 2019.
48. Si YQ, Bian XK, Lu N, Jia YF, Hou ZH and Zhang Y: Cyclosporine induces up-regulation of immunoglobulin-like transcripts 3 and 4 expression on and activity of NKL cells. *Transplant Proc* 44: 1407-1411, 2012.
49. Malaguarnera L: Influence of resveratrol on the immune response. *Nutrients* 11: 946, 2019.
50. Ko JH, Sethi G, Um JY, Shanmugam MK, Arfuso F, Kumar AP, Bishayee A and Ahn KS: The role of resveratrol in cancer therapy. *Int J Mol Sci* 18: 2589, 2017.
51. Ren B, Kwah MX, Liu C, Ma Z, Shanmugam MK, Ding L, Xiang X, Ho PC, Wang L, Ong PS and Goh BC: Resveratrol for cancer therapy: Challenges and future perspectives. *Cancer Lett* 515: 63-72, 2021.
52. Svajger U, Obermajer N and Jeras M: Dendritic cells treated with resveratrol during differentiation from monocytes gain substantial tolerogenic properties upon activation. *Immunology* 129: 525-535, 2010.
53. Acebedo-Martínez FJ, Alarcón-Payer C, Frontera A, Barbas R, Prohens R, Di Crisci M, Domínguez-Martín A, Gómez-Morales J and Choquesillo-Lazarte D: Novel polymorphic cocrystals of the Non-steroidal anti-inflammatory drug niflumic acid: Expanding the pharmaceutical landscape. *Pharmaceutics* 13: 2140, 2021.
54. Jin LH, Kim BH, Lee JH, Lee K, Kwack K and Yim SV: Screening study for genetic polymorphisms affecting pharmacokinetics of talniflumate. *Transl Clin Pharmacol* 25: 166-172, 2017.
55. Altay A, Caglar S and Caglar B: Silver(I) complexes containing diclofenac and niflumic acid induce apoptosis in human-derived cancer cell lines. *Arch Physiol Biochem* 128: 69-79, 2022.
56. Caglar S, Altay A, Kuzucu M and Caglar B: In vitro anticancer activity of novel co(II) and Ni(II) complexes of Non-steroidal Anti-inflammatory drug niflumic acid against human breast adenocarcinoma MCF-7 cells. *Cell Biochem Biophys* 79: 729-746, 2021.
57. Svajger U, Vidmar A and Jeras M: Niflumic acid renders dendritic cells tolerogenic and up-regulates inhibitory molecules ILT3 and ILT4. *Int Immunopharmacol* 8: 997-1005, 2008.

58. Sakata D, Yao C and Narumiya S: Prostaglandin E2, an immuno-activator. *J Pharmacol Sci* 112: 1-5, 2010.
59. Santiso A, Heinemann A and Kargl J: Prostaglandin E2 in the tumor microenvironment, a convoluted affair mediated by EP receptors 2 and 4. *Pharmacol Rev* 76: 388-413, 2024.
60. Tomić S, Joksimović B, Bekić M, Vasiljević M, Milanović M, Colić M and Vučević D: Prostaglandin-E2 potentiates the suppressive functions of human mononuclear Myeloid-derived suppressor cells and increases their capacity to expand IL-10-Producing regulatory T cell subsets. *Front Immunol* 10: 475, 2019.
61. Dunn GP, Koebel CM and Schreiber RD: Interferons, immunity and cancer immunoediting. *Nat Rev Immunol* 6: 836-848, 2006.
62. Saleiro D and Platanias LC: Interferon signaling in cancer. Non-canonical pathways and control of intracellular immune checkpoints. *Semin Immunol* 43: 101299, 2019.
63. Plesca I, Müller L, Böttcher JP, Medyouf H, Wehner R and Schmitz M: Tumor-associated human dendritic cell subsets: Phenotype, functional orientation, and clinical relevance. *Eur J Immunol* 52: 1750-1758, 2022.
64. Baskar R, Lee KA, Yeo R and Yeoh KW: Cancer and radiation therapy: Current advances and future directions. *Int J Med Sci* 9: 193-199, 2012.
65. Alamilla-Presuel JC, Burgos-Molina AM, González-Vidal A, Sendra-Portero F and Ruiz-Gómez MJ: Factors and molecular mechanisms of radiation resistance in cancer cells. *Int J Radiat Biol* 98: 1301-1315, 2022.
66. Sun L, Zhou H, Wu C and Peng Y: Molecular markers that predict response to combined radiotherapy and immunotherapy in patients with lung adenocarcinoma: A bioinformatics analysis. *Transl Cancer Res* 12: 2646-2659, 2023.
67. Chen X, Wang M, Wu F, Lu J, Xiao C, Wu M, Yu J and Chen D: Overcoming Radio-immunotherapy treatment resistance through ILT4 blockade and reversal of HFRT induced CXCL1-CXCR2 axis activation and Tumor-associated macrophage immunosuppression. *Int J Radiat Oncol Biol Phys* 117 (Suppl): S72-S73, 2023.
68. Chen X, Yuan M, Zhong T, Wang M, Wu F, Lu J, Sun D, Xiao C, Sun Y, Hu Y, *et al*: LILRB2 inhibition enhances radiation sensitivity in Non-small cell lung cancer by attenuating Radiation-induced senescence. *Cancer Lett* 593: 216930, 2024.
69. Umiker B, Hashambhoy-Ramsay Y, Smith J, Rahman T, Mueller A, Davidson R, Meyer C, Patankar G, Alam MM, Jaffe S, *et al*: Inhibition of LILRB2 by a novel blocking antibody designed to reprogram immunosuppressive macrophages to drive T-cell activation in tumors. *Mol Cancer Ther* 22: 471-484, 2023.
70. Papadopoulos KP, Lakhani NJ, Yap TA, Naumovski AI, Brown KS, Umiker B, McGrath L, Zhang W, Stack E, Riley G, *et al*: Phase 1, first-in-human trial of JTX-8064, an anti-LILRB2/ILT4 monoclonal antibody, as monotherapy and in combination with anti-PD-1 in adult patients with advanced solid tumors (INNATE). *J Clin Oncol* 39: TPS2672, 2021.
71. Hashambhoy-Ramsay Y, Spaulding V, Priess M, O'Malley K, Gostissa M, Stack E, Smith J, Willer M, Umiker B and Shaffer D: 217 Evaluating biomarkers of JTX-8064 (anti-LILRB2/ILT4 monoclonal antibody) in an ex vivo human tumor histoculture system to inform clinical development. *J Immunother Cancer*: 8, 2020.
72. Cohen H, Hashambhoy-Ramsay Y, Pepper LR, Smith JY, Willer M, Guay K, Spaulding V, O'Malley K, Gostissa M, Dhaneshwar A, *et al*: Preclinical evaluation of JTX-8064, an anti-LILRB2 antagonist antibody, for reprogramming tumor-associated macrophages. *Cancer Res* 79: 5007, 2019.
73. Siu LL, Wang D, Hilton J, Geva R, Rasco D, Abraham AK, Markensohn JF, Suttner L, Siddiqi S, Altura AR and Maurice-Dror C: Initial results of a phase I study of MK-4830, a first-in-class anti-immunoglobulin-like transcript 4 (ILT4) myeloid-specific Antibody in patients (pts) with advanced solid tumours. *Ann Oncol* 31: S462-S462, 2020.
74. Siu LL, Wang D, Hilton J, Geva R, Rasco D, Perets R, Abraham AK, Wilson DC, Markensohn JF, Lunceford J, *et al*: Correction: First-in-class Anti-immunoglobulin-like Transcript 4 Myeloid-Specific Antibody MK-4830 Abrogates a PD-1 Resistance Mechanism in Patients with Advanced Solid Tumors. *Clin Cancer Res* 28: 1734, 2022.
75. Cho BC, Hilton J, Rodriguez CP, Bonomi M, Siu LL, Gil-Martin M, Siddiqi S, Myer NM, Suttner L, Wilson D, *et al*: Abstract CT114: Phase 1 study of the anti-immunoglobulin-like transcript 4 (ILT4) monoclonal antibody MK-4830 plus pembrolizumab in patients with previously untreated advanced head and neck squamous cell carcinoma (HNSCC) or non-small cell lung cancer (NSCLC). *Cancer Res* 84: CT114, 2024.



Copyright © 2025 Cao *et al*. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.