

Discoidin domain receptor tyrosine kinase 2: A new perspective on microenvironment remodeling and targeted therapy of solid tumors (Review)

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Received May 11, 2025; Accepted July 31, 2025

DOI: 10.3892/ol.2025.15279

Abstract. Cancer is one of the major areas on which global medical research and treatment development are currently focused. There has been an increasing incidence of several types of cancer, such as breast cancer, pancreatic cancer, uterine cancer, prostate cancer, liver cancer, kidney cancer, human papillomavirus-associated oral cancer and melanoma. Advancements in biomedical research have expanded treatment options for numerous cancers; however, an ideal or definitive cure remains elusive. Therefore, identifying novel targets for cancer treatment has become a major area of research in biomedicine. Due to its involvement in several human diseases and tumor progression, discoidin domain receptor tyrosine kinase 2 (DDR2) has attracted considerable attention. The present review synthesizes findings from previous studies and highlights the recent advances in DDR2 research, assesses its role across different types of tumors and evaluates its emerging significance in multiple biomedical fields.

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1. Introduction

Cancer remains a major global health problem, with an estimated 19.3 million new cases and ~10 million deaths reported worldwide in 2020 alone (1). The 2024 report of the American Cancer Society projected that 2,001,140 new cancer cases would be diagnosed in the United States in 2024, with an estimated 611,720 deaths (2). Globally, cancer has become the second leading cause of death in the past 100 years (3). Stomach, colorectal, esophageal, pancreatic, ovarian, cervical, kidney, breast, lung, prostate, thyroid and other cancers threaten human health in several ways (4-14). Early detection and timely intervention are crucial for patient prognosis, and early diagnosis and treatment have always been the guiding principles in managing such diseases (15). The detection rate of tumors has increased with the advancements in diagnostic techniques. However, most tumors are detected at an advanced stage, resulting in most patients missing the opportunity for surgical resection treatment. Therefore, determining the target for tumor biotherapy is an essential step in cancer treatment (16,17).

Biomarkers are molecules in the blood, other body fluids or tissues that serve as markers of normal or abnormal processes, conditions or diseases, and can be used to monitor how the body responds to therapy for a certain disease or condition (16). Biomarkers can enable precise and individualized treatment for patients with tumors, thereby opening novel avenues for treating highly heterogeneous neoplastic lesions (18). Classical tumor markers, such as carcinoembryonic antigen, cancer antigen 125 and cancer antigen 19-9, have been widely used in clinical practice and can serve as indicators of biological processes, states or conditions to determine the occurrence, development and prognosis of cancer. However, these markers may also be expressed in nontumor tissues under the influence

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Key words: discoidin domain receptor tyrosine kinase 2, cancer, solid tumor, mechanism, inhibitor

of certain factors (19). Therefore, the identification of sensitive and specific tumor biomarkers is critical for cancer treatment.

Discoidin protein domain receptor (DDR) tyrosine kinases belong to the tyrosine kinase receptor family, which is subdivided into 20 subfamilies based on the homology of ligand-binding extracellular domain features. Abnormalities in these tyrosine kinases are associated with several diseases, including cancer, chronic inflammation and fibrosis (20,21). DDR1 is predominantly expressed in epithelial cells of different tissues, whereas DDR2 is expressed in fibroblasts, myofibroblasts, smooth muscle cells, chondrocytes and other mesenchymal cells (22). In addition, their interaction with MAPK, PI3K, JAK/STAT and Rho-GTPases can induce signal transduction to activate ERK1/2, Akt, cytokine and RhoA-signaling pathways. The DDR2 receptor serves a role in cytoskeletal dynamics, cell proliferation, differentiation, cell survival, adhesion, migration, metabolism, cytokine signaling and immune response (23). In a previous study, the expression of DDR2 on tumor-associated fibroblasts increased the hardness of tumor tissues (24).

The present review summarizes the latest research progress on DDR2, its role in cancer and its underlying mechanisms of action, including its abnormal expression in cancer and its prognostic value. Additionally, the current status of global drug and future design prospects for DDR2 are also reviewed.

2. Structure and function of DDR2

The molecular structure of DDR includes an extracellular binding domain, a transmembrane domain and an intracellular kinase domain. The extracellular binding domain is composed of a discoidin (DS) domain and a DS-like domain for collagen binding (25). The DDR2 gene is located on human chromosome 1 (1q23.3) and consists of 19 exons, of which exons 4-19 are transcribed into a mRNA transcript that is then translated to produce the DDR2 protein product. Connective tissue cells originating from the embryonic mesoderm can be stimulated and activated by collagen types I, II, III and X, and they participate in several physiological and pathological processes. The extracellular binding region of DDR2 consists of N-terminal DS domains that can bind to collagen, DS-like domains and extracellular phagocyte membrane regions, providing N- and O-glycosylation sites and MMP cleavage sites. N- and O-glycosylation sites are important sites for the glycosylation of DDR2. The glycosylation modification of DDR2 can enhance its signal-conduction ability (26). The MMP cleavage sites of DDR2 are associated with the mutual regulation between DDR2 and MMPs (27). MMPs can cleave several substrates, including cell surface receptors. Therefore, the presence of MMP cleavage sites in DDR2 can lead to the cleavage and inactivation of DDR2 by MMPs, thereby regulating the activity of DDR2 (28). DDR2 can act in conjunction with myosin IIA to regulate the adhesion and traction of collagen and condense collagen fibrils into a denser arrangement, thereby reshaping the generation and arrangement of collagen fibers (29).

3. Expression of DDR2 in human single cells

For further analysis, the present study mapped the DDR2 in tissues, cells and organs using the Human Protein Atlas (HPA)

database (www.proteinatlas.org), which integrates proteomics, transcriptomics and systems biology data. The results revealed that DDR2 was most abundant in nontumor cells in the single-celled expression cluster (<https://www.proteinatlas.org/ENSG00000162733-DDR2/cell+line>). Furthermore, the RNA expression levels of DDR2 in several tissues were summarized using the HPA database (<https://www.proteinatlas.org/ENSG00000162733-DDR2/tissue>).

4. Research progress of DDR2 in solid tumors

DDR2 is abnormally expressed in numerous human solid tumors and has been associated with tumorigenesis. The current research results of DDR2 in several solid tumors are summarized in Table I.

Furthermore, analysis of data from the Tumor Immune Estimation Resource database (<http://cistrome.org/TIMER/>) revealed that the DDR2 expression was different across breast duct carcinoma with subsequent lung adenocarcinoma, breast cancer, colon adenocarcinoma, kidney chromophobe, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, prostate adenocarcinoma, rectal adenocarcinoma, skin cutaneous melanoma, thyroid carcinoma, uterine corpus endometrial carcinoma and other cancers (Fig. 1). In addition, a literature search revealed the involvement of DDR2 in ovarian, breast, lung, colorectal and other cancers through several pathways (30-33). Several functions of DDR2 in solid tumors are presented in Fig. 2.

5. DDR2 in the tumorigenesis mechanism

DDR2 in ovarian cancer. Ovarian cancer is a highly prevalent malignant tumor, and its incidence ranks eighth among female tumors in the world. Worldwide, 314,000 cases and 207,000 deaths have been reported annually. Furthermore, the incidence of most cancers is decreasing in Northern Europe and North America based on age markers; however, it is on the rise in certain parts of Eastern Europe and Asia (34,35). In a recent study, Schab *et al* (36) reported that the expression of DDR2 is negatively associated with the survival rate of patients with ovarian cancer.

DDR2 can facilitate ovarian cancer metastasis and enhance tumor invasion by regulating the metabolism and secretion of extracellular matrix (ECM) proteins. Cancer-associated fibroblasts (CAFs) are major matrix components in the tumor microenvironment (TME). CAFs exhibit considerable heterogeneity and plasticity, and have a marked effect on the immune response and metabolic reprogramming within the TME, thereby influencing tumor progression (37). Akinjiyan *et al* (38) reported that DDR2 expressed by CAFs enhances collagen production and tumor progression by regulating arginase activity, indicating that DDR2 and arginase in CAFs are likely targets in ovarian cancer. This process involves the activation of the transcription factor SNAIL1, which induces epithelial-mesenchymal transition (EMT) of tumor epithelial cells (39,40). In addition, DDR2 can regulate the expression of SNAIL1, affect the expression of arginase 1, and influence the occurrence and development of tumors. Cisplatin is a well-established chemotherapeutic drug in the treatment of several human cancers (41), but its extensive clinical use in treating tumors often leads to chemical resistance,

Table I. Research progress of discoidin domain receptor tyrosine kinase 2 in several solid tumors.

A, Ovarian cancer			
First author, year	Result	Mechanism	(Refs.)
Schab <i>et al</i> , 2023	Promotes ovarian cancer metastasis	Regulates metabolism and secretion of extracellular matrix proteins	(36)
Akinjiyan <i>et al</i> , 2024	Promotes tumor growth	DDR2 expressed by CAFs promotes collagen production and tumor progression by regulating arginase activity	(38)
Heiserman <i>et al</i> , 2021	Promotes tumor resistance	XI α 1 collagen up-regulates the expression and activity of HSP27 through DDR2/integrin α 1 β 1-Src-Akt signaling pathway, inducing cisplatin resistance in ovarian cancer cells	(43)
B, Breast cancer			
First author, year	Result	Mechanism	(Refs.)
Corsa <i>et al</i> , 2016	Promotes breast cancer metastasis	DDR2 can reshape the extracellular matrix by affecting TME and promoting breast cancer metastasis	(45)
Lin <i>et al</i> , 2021	Increases susceptibility to iron death	DDR2 upregulation increases susceptibility to iron death in recurrent breast tumors via the Hippo pathway	(46)
C, Gastric cancer			
First author, year	Result	Mechanism	(Refs.)
Kurashige <i>et al</i> , 2016	Promotes peritoneal metastasis of gastric cancer	Dasatinib, a DDR2 inhibitor, reduces peritoneal metastasis in gastric cancer	(54)
Wang <i>et al</i> , 2016	Promotes the growth of gastric cancer	The mTORC2/Akt signaling pathway promotes epithelial mesenchymal transformation to promote the occurrence and development of gastric cancer	(55)
D, Colorectal cancer			
First author, year	Result	Mechanism	(Refs.)
Firouzjaei <i>et al</i> , 2023	Associated with the prognosis of colorectal cancer	Analysis using the GEPIA and GEO databases	(56)
Xu <i>et al</i> , 2023	Promotes metastasis of colorectal cancer	Regulating epithelial stromal transformation through activation of AKT signaling	(60)
E, Hepatocellular carcinoma			
First author, year	Result	Mechanism	(Refs.)
Xie <i>et al</i> , 2015	Promotes the invasion and migration of hepatocellular cancer cells	Activate ERK signal and stabilize SNAIL1	(65)
Liu <i>et al</i> , 2024	Oxaliplatin resistant	Overexpression of immunosuppressive checkpoints such as PD-L1 PD-and CD155 via DDR2/STAT3 positive feedback loops prevents CD8+ T cell-mediated immunokilling; and the secretion of chemokine CCL20 recruits MDSCs into the tumor microenvironment, thereby establishing an immune tolerance environment	(70)

Table I. Continued.

E, Hepatocellular carcinoma			
First author, year	Result	Mechanism	(Refs.)
Li <i>et al</i> , 2023	Resistant to sorafenib	Sorafenib resistance is mediated through the NF- κ B/c-Rel signaling pathway	(72)
Cai <i>et al</i> , 2022	Promotes hepatocellular cancer cell metastasis	Activation of the DDR2/ β -catenin pathway	(75)
F, Neuroblastoma			
First author, year	Result	Mechanism	(Refs.)
Rozen <i>et al</i> , 2024	Control of the meta-stasis of neuroblastoma	Sitravatinib blocks DDR2 to control the metastasis of neuroblastoma	(79)
G, Thyroid cancer			
First author, year	Result	Mechanism	(Refs.)
Liang <i>et al</i> , 2017	DDR2 promotes the occurrence and growth of thyroid cancer through EMT	Activation of ERK2 increases the protein level of Snail1 and induces EMT in thyroid papillary carcinoma	(82)
H, Prostate cancer			
First author, year	Result	Mechanism	(Refs.)
Yan <i>et al</i> , 2014	Promotes the bone metastasis of prostate cancer	By regulating the phosphorylation and exchange activity of RUNX2, regulating the expression of PTHrP promotes bone metastasis of prostate cancer	(87)
I, Urothelial carcinoma			
First author, year	Result	Mechanism	(Refs.)
Tsai <i>et al</i> , 2016	DDR2 is associated with a poor prognosis of urothelial carcinoma	Urothelial carcinoma tissue expresses DDR2, and combined with clinicopathological data, the survival of patients with low DDR2 expression was greater than that of patients with high expression	(89)
J, Melanoma			
First author, year	Result	Mechanism	(Refs.)
Poudel <i>et al</i> , 2015	Increases the migration and invasion of melanoma cells	DDR2 regulates the production of MMP2/MMP9 in type I collagen response by regulating ERK and NF- κ B signaling pathways, thereby modulating the mechanisms of cell migration and invasion phenotypes	(92)

DDR2, discoidin domain receptor tyrosine kinase 2; CAFs, cancer-associated fibroblasts; HSP27, heat shock protein 27; TME, tumor micro-environment; GEPIA, Gene Expression Profiling Interactive Analysis; GEO, Gene Expression Omnibus; PD-L1, programmed death-ligand 1; CCL20, C-C motif chemokine ligand 20; EMT, epithelial-mesenchymal transition; RUNX2; PTHrP, parathyroid hormone-associated protein; MDSC, myeloid-derived suppressor cell.

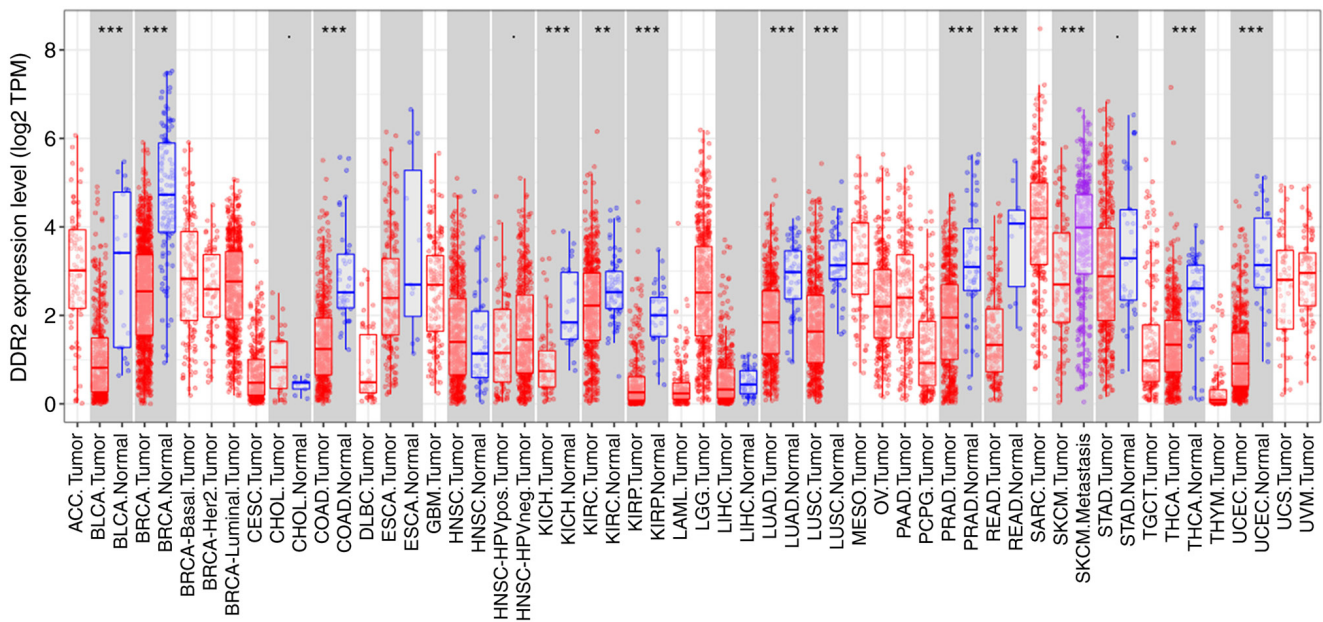


Figure 1. Differential expression of DDR2 between different cancer tumors and normal tissues. Distributions of gene expression levels are displayed using box plots. The statistical significance was assessed using the Wilcoxon rank-sum test. ** $P < 0.01$; *** $P < 0.001$. DDR2, discoidin domain receptor tyrosine kinase 2; TPM, transcripts per million.

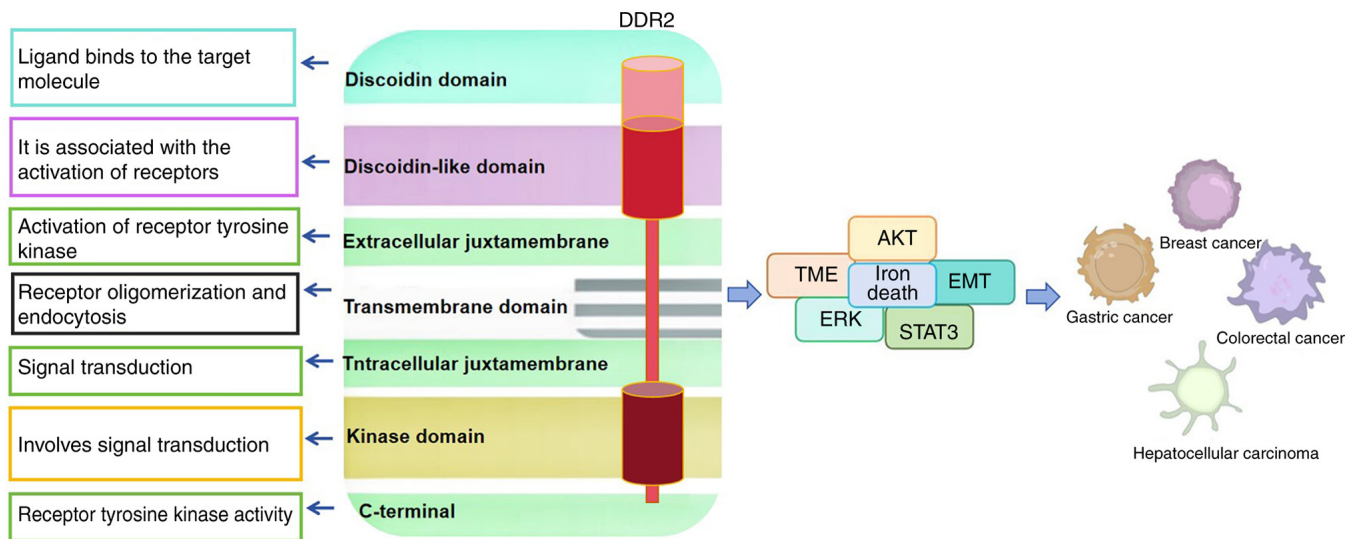


Figure 2. Functions of DDR2 in certain solid tumors. DDR2 promotes the progression of cancer cells through multiple pathways in several tumors. DDR2, discoidin domain receptor tyrosine kinase 2; TME, tumor microenvironment; EMT, epithelial-mesenchymal transition.

namely, drug resistance (42). Studies on this drug have received notable attention. For instance, Heiserman *et al* (43) reported that type XI α 1 collagen confers cisplatin resistance in ovarian cancer by upregulating heat shock protein 27 expression and activity through the DDR2/integrin α 1 β 1-Src-Akt-signaling pathway. Therefore, according to research findings on the role of DDR2 in ovarian cancer, this receptor can not only promote the occurrence and metastasis of tumors, but also increase the drug resistance of tumors through other mechanisms. Thus, DDR2 is a promising biomarker in ovarian cancer.

DDR2 in breast cancer. Breast cancer is a major health problem among women worldwide. It is characterized by

‘cold tumors’ exhibiting low levels of immune cell infiltration, which limits the efficacy of conventional immunotherapy. At present, research is focused on the strategy of transforming a ‘cold tumor’ into a ‘hot tumor’ through the TME (44).

In a recent study on DDR2, Corsa *et al* (45) noted that, during the occurrence, progression and metastasis of breast tumors, both tumors and tumor-related stromal cells can express DDR2 and reshape the ECM, thereby altering the TME and promoting breast cancer metastasis. Moreover, in a study by Lin *et al* (46), DDR2 upregulation was reported to increase the susceptibility of recurrent breast tumors to iron-dependent cell death or ferroptosis through the Hippo pathway. Ferroptosis refers to the iron-dependent lethal accumulation of membrane

lipid peroxides. This process is a form of regulated cell death that has received attention from the research community since its proposal by Brent R. Stockwell in 2012 (47). This study experimentally demonstrated that the high sensitivity of breast tumors to iron is attributable to the overexpression of DDR2 in breast tumor cells with mesenchymal characteristics. The study also reported that increased DDR2 levels may serve as the molecular basis for EMT and that there is an association between mesenchymal characteristics and sensitivity to ferroptosis in recurrent breast cancer. This seemingly forms a closed-loop mechanism. Although increased DDR2 expression promotes breast cancer recurrence, it also enhances tumor susceptibility to ferroptosis, thus providing new clues for treating recurrent breast cancer.

Furthermore, triple-negative breast cancer is characterized by the absence of endocrine therapeutic targets and human epidermal growth factor receptor 2 blockade, and it has a poor prognosis (48). Current research on this disease aims to identify specific molecular and genetic markers (49). Notably, DDR2 is expressed in human triple-negative breast tumors and tumor stroma, potentially providing a new target for the treatment and diagnosis of this disease (50).

DDR2 in gastric cancer. Gastric cancer, also known as stomach cancer, is a highly malignant and common digestive tract tumor. Advancements in surgical techniques and the development of antitumor drugs have improved the prognosis of patients with gastric cancer. However, the survival rate and quality of life of these patients are still lower than those of patients with colorectal cancer, liver cancer and other digestive tract tumors (51). Peritoneal metastasis (PM) is common in gastric cancer, and it has been reported that >50% of the patients have PM at the time of death (52). The 5-year survival rate of patients with gastric cancer with PM is ~2%, and the median survival time is 3-5 months (53).

A study by Kurashige *et al* (54) using four gastric cancer cell lines, reported the association of DDR2 with poor prognosis and peritoneal dissemination of gastric cancer. It also demonstrated that the DDR2 inhibitor dasatinib can reduce gastric cancer PM. Wang *et al* (55) combined the analysis of immunohistochemistry results and clinicopathological data, and reported that DDR2 expression was associated with adverse clinicopathological features in patients with gastric cancer. The study further demonstrated that the receptor stimulates epithelial transformation via the mTORC2/Akt-signaling pathway, thereby promoting the occurrence and development of gastric cancer (55).

DDR2 in colorectal cancer. Colorectal cancer is the second leading cause of cancer-related death worldwide. Firouzaei *et al* (56), using the Gene Expression Profiling Interactive Analysis and Gene Expression Omnibus databases, reported that DDR2 expression was associated with the prognosis of colorectal cancer. Currently, metastatic colorectal cancer is a serious clinical problem, and despite having surgery and chemotherapy as treatment options, it has a poor prognosis.

DDR1 and DDR2 may serve as potential therapeutic targets for metastatic colorectal cancer (57-59). In a study by Xu *et al* (60), high DDR2 expression was associated with a low survival rate, and patients with a higher expression of DDR2

had worse overall survival. In addition, DDR2 may promote colorectal cancer metastasis through the activation of AKT signaling by regulating epithelial-stromal transformation. Therefore, the early detection of DDR2 expression in patients with colorectal cancer may aid in the clinical diagnosis and treatment of this cancer.

DDR2 in hepatocellular carcinoma (HCC). HCC is a primary malignant tumor of the liver and is usually diagnosed at an advanced stage when the tumor is unresectable. In such cases, systemic treatment with tyrosine kinase inhibitors is the primary option (61). Although α -fetoprotein has been used as a clinical indicator for the diagnosis and prognosis assessment of liver cancer, the development of new biomarkers remains a focus of HCC research (62).

Research findings have revealed that downregulating DDR2 expression can reduce the proliferation and migration of HCC cells (63,64). Xie *et al* (65) assessed the expression of DDR2 in the normal liver LO2 cell line, and the liver cancer SMMC-7721, Huh-7, HepG2, Hep3B and MHCC97-H5 cell lines, and reported that whilst DDR2 expression was low in normal liver LO2 cells, it was increased in the other five HCC cell lines. Additionally, the expression of DDR2 in the highly aggressive metastatic HCC cell line (MHCC97-H5) was reported to be notably higher than that in less aggressive HCC cell lines. Additionally, Cox regression analysis of the clinical data suggested that DDR2 is an independent prognostic factor for HCC. Furthermore, DDR2 was reported to promote cell invasion, migration and EMT by activating ERK signaling, stabilizing SNAIL1 and upregulating the expression of membrane type MMP and MMP2 via the ERK2/SNAIL1 signaling pathway (65).

Immunotherapy is a valuable approach to HCC treatment. Programmed cell death protein-1 (PD-1) is a checkpoint receptor expressed on the surface of several immune cells. PD-L1 is a natural receptor of PD-1 and is predominantly expressed in tumor cells. PD-1 and PD-L1 are closely associated with the progression of human cancer (66). In the liver of patients of HCC, PD-L1 is mainly expressed in tumor cells, Kupffer cells and hepatocytes (67). The activation of the STAT3 signaling pathway can directly and indirectly induce the expression of PD-L1 (68). Oxaliplatin is a commonly used platinum-based chemotherapeutic drug (69); however, as with several other drugs used in tumor chemotherapy, drug resistance has become the most notable problem limiting its effect.

Liu *et al* (70) reported that DDR2 and STAT3 create an immunosuppressive microenvironment by upregulating PD-L1 expression and recruiting myeloid-derived suppressor cells (MDSCs) through a positive feedback loop, leading to drug resistance in HCC. DDR2 was found to be highly expressed in drug-resistant HCC, interacts with STAT3 and promotes STAT3 phosphorylation. In addition, the receptor increases liver cancer cell proliferation and oxaliplatin resistance through STAT3 signaling, thereby stimulating HCC development by increasing DDR2 expression (70). MDSCs are a heterogeneous group of immature myeloid cells with immunosuppressive activity (71). Oxaliplatin-resistant cells overexpress immunosuppressive checkpoint proteins such as PD-L1 and CD155 through DDR2/STAT3-positive feedback loops, thus preventing CD8⁺ T-cell-mediated immune killing. Notably, oxaliplatin-resistant cells secrete the chemokine C-C motif chemokine ligand 20

(CCL20) to recruit MDSCs into the TME, thereby establishing an immune-tolerant environment. Sorafenib, a multikinase inhibitor that promotes apoptosis, alleviates angiogenesis and inhibits tumor cell proliferation, is the first-line treatment option for HCC. As a result, the mechanism of resistance to this drug has attracted extensive research attention (72,73). DDR2 has been reported to mediate sorafenib resistance through the NF- κ B/c-Rel-signaling pathway (74). Moreover, as DDR2 has been reported to induce liver cancer growth and drug resistance, it may also serve as a link to the mechanism pathway, mediating other factors to promote the development of liver cancer. For example, Cai *et al* (75) reported that the long noncoding RNA CEBPA-DT promotes liver cancer metastasis by activating the DDR2/ β -catenin signaling through interaction with heterogeneous nuclear ribonucleoprotein C.

DDR2 in neuroblastoma. Neuroblastoma is a cancer that arises from neural crest cells and is the most common extracranial solid tumor in children (76). Research by Vessella *et al* (77) reported that DDR2 is required for the normal proliferation of neuroblastoma cells and that DDR2 signaling and mechanical sensing regulate the growth of neuroblastoma cells by several transcriptomic mechanisms. In neuroblastoma, the action of sitravatinib, an immunoregulatory multitarget kinase inhibitor (78), was reported to be mediated by DDR2. This drug blocks DDR2 to inhibit the metastasis of neuroblastoma (79).

DDR2 in thyroid cancer. Thyroid cancer is the most common endocrine malignancy, and most cases are diagnosed early, are highly differentiated and have a good prognosis (80). Papillary carcinoma accounts for ~80% of thyroid cancers, and the increase in thyroid cancer incidence can almost entirely be attributed to the increase in papillary thyroid cancer (81).

Liang *et al* (82) studied the mechanism of DDR2 in thyroid cancer, and reported that, as in other cancers, DDR2 promotes the occurrence and development of thyroid cancer through EMT. DDR2 specifically activates ERK2 to increase the protein expression of SNAIL1 to induce EMT in papillary carcinoma.

DDR2 in prostate cancer. Prostate cancer is a type of urologic cancer that forms in the prostate, with a relatively high incidence worldwide, and it is the second-most common cancer in men after lung cancer (83). Although prostate-specific antigen is widely used as a clinical marker for prostate cancer, it lacks specificity. Thus, prostate cancer biomarkers continue to be the focus of current research (84).

Azemikhah *et al* (85) reported that DDR2 is differentially expressed in prostate cancer tissues compared with that in noncancerous prostate tissues. The mRNA expression of DDR2 is upregulated in advanced prostate cancer and prostatic hyperplasia tissues. Furthermore, the expression of DDR2 mRNA and protein in advanced prostate cancer tissues was associated with prognostic factors. Additionally, an analysis of The Cancer Genome Atlas database by Huang *et al* (86) revealed that DDR2 is associated with disease diagnosis in patients with prostate cancer. A study by Yan *et al* (87) also reported that DDR2 promotes prostate cancer bone metastasis by regulating the phosphorylation and the exchange activity of RUNX family transcription factor 2, thereby regulating the expression of parathyroid hormone-related protein.

DDR2 in urothelial carcinoma. The most common pathological subtype of bladder and upper urinary tract malignancies is urothelial carcinoma (88). In a large cohort study, DDR2 was reported to be overexpressed in upper urinary tract urothelial carcinoma and urinary bladder urothelial carcinoma. When combined with clinicopathological data, DDR2 was associated with the poor prognosis of urothelial carcinoma, and the survival of patients with low expression of DDR2 was reported to be higher than that of those with high expression (89).

DDR2 in melanoma. Although DDR1 is the primary DDR in the epidermis, where it is involved in melanocyte homeostasis, DDR2 appears to be the primary DDR implicated in melanoma (90). In addition, DDR2 controls cell and tumor proliferation via the MAP kinase pathway *in vitro* and *in vivo* in drug-resistant cells. Therefore, inhibiting DDR2 may represent a novel strategy to combat the resistance mechanism (91). Poudel *et al* (92) reported that DDR2 regulates the production of MMP2/9 in type I collagen response by regulating the ERK and NF- κ B signaling pathways, thereby modulating cell migration mechanisms and invasion phenotypes. Therefore, DDR2 is a receptor tyrosine kinase with notable therapeutic potential for melanoma (92).

6. DDR2 and the TME

The TME refers to the noncancerous cells and their components present in the tumor environment, including fibroblasts, endothelial cells, neurons, fat cells, adaptive cells and innate immune cells. This term also refers to the continuous interaction between tumor cells and the TME, which serves a decisive role in the cancer development, progression and metastasis, as well as in the therapeutic response of the tumor (93,94). The ECM is an important component of the TME. Tumor cells interact with the ECM to promote cancer cell proliferation, migration, invasion, angiogenesis and immune escape; thus, the ECM has become a key target in cancer treatment (95,96). The ECM is mainly composed of proteoglycans, glycoproteins, matrix proteins, osteopontin, thrombo-reactive protein and structural proteins, which undergo dynamic remodeling to maintain the TME (97,98). DDR2 is uniquely positioned to act as an ECM sensor and can be activated by ECM collagen-induced binding protein receptors. Processes such as migration, proliferation and cytokine secretion are regulated, leading to ECM remodeling and reconstruction in an unbalanced homeostasis (24,99). DDR2-expressing CAFs can promote metastasis of ovarian cancer by influencing ECM remodeling (100).

7. DDR2 and CAFs

The population of fibroblasts found in both primary and metastatic cancers is collectively referred to as CAFs. They are the most abundant cell types in the TME and are the central hub of cross-communication among several cells in the tumor stroma (101,102). Aside from being highly heterogeneous, CAFs are differentially expressed in different tumor tissues, and several CAF subtypes have been identified in numerous cancers. Targeted CAF therapy is currently a research hotspot in antitumor therapy. In CAFs, DDR2 expression is directly associated with their ability to reshape

Table II. Clinical trials of discoidin domain receptor tyrosine kinase 2.

Project name	Drug name	Recruitment status
Phase II trial of dasatinib in subjects with advanced cancers harboring DDR2 mutation or inactivating B-RAF mutation	Dasatinib	Recruitment cancellation
Phase II trial of dasatinib in subjects with advanced cancers harboring DDR2 mutation or inactivating B-RAF mutation	Dasatinib	Terminated
An exploratory clinical trial of PET-MRI application of ⁶⁴ Cu-DDR2 vs. ¹⁸ F-PDG in preoperative diagnosis of newly diagnosed glioblastoma	-	Not yet started
Prospective, single-arm, multicenter clinical study of the efficacy and safety of dasatinib for imatinib treatment failure in fibroids	Dasatinib	Not yet started

DDR2, discoidin domain receptor tyrosine kinase 2.

the ECM (103,104). For example, a previous study reported that DDR2-expressing CAFs regulate periostin (POSTN) protein via integrin subunit B1 (ITGB1), promoting ovarian cancer metastasis. DDR2 and POSTN signal through the PI3K/AKT and Src pathways and can serve as potential therapeutic targets for ovarian cancer (105). In a breast cancer study, DDR expression by CAFs increased the aggressiveness of breast tumor cells through regulation of the basement membrane and paracrine signaling. Based on these findings, the study indicated that the independent tyrosine kinase activity of DDR2 in breast tumor cells and breast tumor CAFs regulates breast cancer metastasis. Therefore, adjuvant therapy targeting tyrosine kinase activity should not only target tumor cells and stromal cells but also target the tumor stromal cells. Furthermore, drugs that inhibit tyrosine kinase-dependent and tyrosine kinase-independent effects are urgently needed (106).

8. DDR2 and immunotherapy

To date, immune checkpoint-targeted drugs, such as anti-cytotoxic T lymphocyte-associated protein 4, anti-PD-1 and anti-PD-L1, as well as other new targeted drugs, have achieved notable results in several cancer immunotherapies. However, accumulating evidence suggests that positive response rates remain low in patients receiving immune checkpoint-targeted drugs and drug resistance emerges, which is an issue that warrants attention (107,108). DDR1 and DDR2 have been identified as potential therapeutic targets for MAPK inhibitor resistance, and mutations in DDR2 have shown particular efficacy with dasatinib in squamous cell lung carcinoma (109,110). The tumor immune microenvironment is composed of tumor cells, immune cells and cytokines. These components can be classified as antitumor and protumor, and the interaction between them determines the trend of antitumor immunity (111). These reported findings demonstrate that DDR2 is involved in multiple mechanisms mediating the interactions between tumor cells and immune cells, and thus immunotherapy targeting DDR2 may provide new perspectives to tumor therapy.

9. Co-activation pathway of DDR2 in different solid tumors

EMT refers to the cellular process through which epithelial cells lose their properties and gain interstitial properties to facilitate cell movement. This process is abnormally activated in human cancers and contributes to enhanced tumor initiation, cell migration, invasion, metastasis and therapeutic resistance (112). DDR2 is expressed in interstitial cells and can be activated by collagen, thus we hypothesize that DDR2 is associated with organ fibrosis and EMT. DDR2 can promote tumor metastasis and invasion through EMT in ovarian cancer, breast cancer, stomach cancer, colorectal cancer, thyroid cancer and other cancers (37,38,43,53,58,80). Therefore, as DDR2 can promote tumor metastasis and invasion, therapies targeting the tumor microenvironment in patients with cancer with high DDR2 expression may be effective.

10. Current status of research on drugs and antibodies targeting DDR2

Due to its potential use in antitumor therapy, several drugs targeting DDR2 have been developed and used in clinical trials and research. The present review used the Pharnexcloud Cloud database (<https://www.pharnexcloud.com/>) to retrieve information on DDR2 global clinical trials (Table II) and drug development (Table III) (113-118). In addition, the prognostic value of DDR2 in solid tumors was also summarized in Table IV.

11. Strengths of the present review

Table V provides a comparison between the present review and the study by Trono *et al* (119). Moreover, the present review included multiple studies on DDR2 with the aim of including more innovations. The strengths of the present review are as follows: i) The review systematically outlines the role of DDR2 in several solid tumors, such as ovarian cancer, breast cancer, gastric cancer and liver cancer (a total of 12 categories). The expression, function and clinical significance of DDR2 in each cancer type are listed in Table I; ii) the

Table III. Current research on drugs targeting DDR2.

Drug	Research field	Indication	Highest research and development stage	(Refs.)
CIDD-0108633	Tumor	Pancreatic ductal adenocarcinoma	Preclinical	(113)
ICP-033	Tumor	Advanced solid tumor, colorectal cancer, liver tumor and renal cell tumor	Phase I clinical	(114)
BK-40143	Neural research	Alzheimer's disease	Preclinical	(115)
PB-1	Tumor	Squamous cell carcinoma	Preclinical	(116)
Dual DDR-1/2 inhibitors	Acute lung injury and autoinflammatory disease	Respiratory system and inflammation	Drug discovery	(117)
Dasatinib	Acute lymphoblastic leukemia, chronic myeloid leukemia, glioblastoma, triple-positive breast cancer, breast cancer, hormone receptor negative breast cancer, lymphoplasmacytoid lymphoma/immunocytoma, metastatic breast cancer, metastatic non-small cell lung cancer and triple-negative breast cancer	-	Preclinical	(118)

DDR-1/2, discoidin domain receptor tyrosine kinase 1/2.

present review describes the single-cell expression profile of DDR2 in nontumor cells based on the HPA database, emphasizing its specific distribution in stromal cells and providing a cell-type basis for targeted therapy; iii) the present review describes the current status of clinical trials, drug and antibody research, and development of anti-DDR2 drugs using databases such as Pharnexcloud; iv) the present review offers the following mechanistic innovations: It proposes a new mechanism by which the DDR2-Hippo pathway regulates ferroptosis, and also explains that, although high expression of DDR2 promotes breast cancer recurrence, it also enhances the sensitivity of tumor cells to ferroptosis, thus providing a new idea for combined targeted therapy. Moreover, it identifies a new axis of immune resistance in liver cancer, observing that the DDR2/STAT3/PD-L1 positive feedback loop mediates oxaliplatin resistance. It also describes that the recruitment of MDSC by CCL20 creates an immunosuppressive micro-environment that promotes immune escape; v) the present review identifies a new target of stromal cell, revealing that in CAFs DDR2 regulates POSTN through ITGB1 to promote ovarian cancer metastasis, and also highlights the therapeutic value of targeting the DDR2-POSTN-PI3K/Akt axis; and vi) the present review focuses on clinical transformation and unsolved issues by associating DDR2 with chemotherapy resistance (such as cisplatin resistance in ovarian cancer and sorafenib resistance in liver cancer), proposing new pathways

(such as DDR2/NF- κ B/c-Rel signaling) and guiding the design of combination therapy; and proposing the combination of DDR2 inhibitors and PD-1/PD-L1 antibodies to reverse 'cold tumors' (such as breast cancer) and exploring its potential to affect T-cell infiltration by regulating collagen arrangement. In summary, the primary strength of the present review lies in its integration of multi-cancer clinical data, systematic analysis of drug resistance mechanisms and comprehensive review of current therapeutic developments targeting DDR2. It addresses the gaps in cancer-type coverage in other reviews and aligns more closely with the practical needs of clinicians and researchers in translational medicine. Although available studies on DDR2 emphasize mechanistic explorations, the present review broadens the scope by incorporating clinical data and cross-cancer analyses, thereby expanding potential applications. The information provided in the present review offers notable practical value for clinical decision-making. Furthermore, the review complements other investigations in the field and contributes to advancing DDR2 research in both basic science and clinical settings.

12. Conclusions and perspectives

Several studies have reported that DDR2 serves different pivotal roles in numerous types of solid tumor, especially through ECM and CAFs. It also participates in multiple

Table IV. Prognostic value of discoidin domain receptor tyrosine kinase 2 in solid cancers.

First author, year	Cancer	Association with prognosis	Prognostic result	(Refs.)
Schab <i>et al.</i> , 2023	Ovarian cancer	Expression of DDR2 is associated with the survival rate of patients	Higher the expression of DDR2 is associated with a lower survival rate	(36)
Lin <i>et al.</i> , 2018	Breast cancer	DDR2 expression is associated with recurrent breast cancer	Increase of DDR2 expression promotes the recurrence of breast cancer	(46)
Kurashige <i>et al.</i> , 2016	Gastric cancer	DDR2 expression is associated with adverse types and survival rate of gastric cancer	Higher expression of DDR2 is associated with a lower survival rate	(54)
Xu <i>et al.</i> , 2023	Colorectal cancer	DDR2 expression is associated with the survival rate	Higher expression of DDR2 is associated with a lower survival rate	(60)
Xie <i>et al.</i> , 2015	Hepatocellular carcinoma	DDR2 is an independent prognostic factor for hepatocellular carcinoma	DDR2 expression increases the invasiveness of hepatocellular carcinoma	(65)
Tsai <i>et al.</i> , 2018	Urothelial carcinoma	DDR2 expression is associated with survival rate	Survival period of patients with low expression of DDR2 is longer than that of patients with high expression	(89)

DDR2, discoidin domain receptor tyrosine kinase 2.

Table V. Innovative summary.

First author, year	Research focus	Type of cancer	Mechanism	Treatment strategy	Data source	(Refs.)
Trono <i>et al.</i> , 2024	Molecular mechanism of DDR2, micro-environment remodeling and the synergy of immunotherapy	Breast and ovarian cancer	DDR2-collagen positive feedback loop; formation mechanism of invasive pseudopodia; and kinase-independent function	Novel inhibitor (WRG-28) and combined immunotherapy	Original experimental data integration and cBioPortal mutation analysis	(119)
Present study	Cancer-specific effects, clinical transformation and drug resistance mechanisms of DDR2	>12 types of cancer, e.g., gastric cancer, colorectal cancer and hepatocellular carcinoma	EMT and drug resistance pathways (STAT3/PD-L1)	Existing drug applications (dasatinib) and antibody development	Public databases (TIMER/HPA) and literature reviews	-

DDR2, discoidin domain receptor tyrosine kinase 2; EMT, epithelial-mesenchymal transition; PD-L1, programmed death-ligand 1; TIMER, Tumor Immune Estimation Resource; HPA, Human Protein Atlas.

mechanisms to promote tumor metastasis and drug resistance. Both ECM and CAFs, as well as EMT, are a major focus of tumor research. As the research on DDR2 progresses, biological processes involved in tumor occurrence and development are likely to be revealed. In addition, as the potential of DDR2 inhibitors continues to be investigated through drug development and clinical trials, new perspectives are likely to emerge in the treatment of tumors.

The present article offers a comprehensive and insightful review of DDR2 as a promising target in solid tumors. It examines key aspects, including the structure and function of DDR2, its expression in several tissues and tumors, and its role in the tumorigenesis of different types of cancer, such as ovarian, breast and stomach cancers. This broad coverage is useful for researchers looking for a comprehensive resource for DDR2 in solid tumors. Additionally, it bridges the gap between basic research and clinical application by assessing the current global progress on DDR2 drugs and antibodies, which is crucial for translating laboratory findings into potential cancer treatments. Finally, the present review provides potential new directions for the pursuit of effective cancer treatments through DDR2-targeted strategies.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Regional Science Foundation Project of the National Natural Science Foundation of China (grant nos. 82160111 and 82360115) and the Targeted Exploration Project of the Medical Department of Lanzhou University (grant no. lzuyxcx-2022-181).

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

TL designed and wrote the article and searched for relevant literature. HGu revised the article and searched for relevant literature. HGo and YM refined the language. YT and DZ revised the article. TL and DZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

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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