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Running title: The role of DDR1 in cancer

Research progress on the role of DDR1 in cancer and targeted therapy strategy

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Discoidin domain receptor 1 (DDR1) is a receptor tyrosine kinase activated by various types of collagen. Abnormal activation of DDR1 is closely related to the occurrence and development of solid tumors and plays an important role in the regulation of cell adhesion, survival, proliferation, migration, and invasion. Thus, DDR1 is a promising therapeutic target in the field of oncology. This review introduces the structural characteristics of DDR1, focusing on its role in tumor progression and related signaling pathways. It also explores the relationship between DDR1 and tumor chemotherapy resistance, and elaborates on the current research status and development prospects for inhibitors and antibodies targeting DDR1. Thus, the DDR1 inhibition strategy may serve as a new alternative for treating cancer patients.

Key words: DDR1; cancer progression; targeted therapy; selective inhibitors

Discoidin domain receptors (DDRs) were discovered in the slime mold, *Dictyostelium discodium* in the early 1990s [1]. DDRs activation is triggered by various forms of collagen. DDR1 plays a vital role in the progression of cancer, participating in regulating multiple cellular processes such as tumor cell proliferation, migration, metabolism, epithelial-mesenchymal transition (EMT), and matrix remodeling, ultimately affecting the survival of patients with cancer. In recent years, various small-molecule tyrosine kinase inhibitors targeting DDR1 have been developed.

The structure and activation of DDR1

DDRs belong to a family of receptor tyrosine kinases (RTKs) with two subtypes: DDR1 and DDR2. These two types of DDRs can be activated by various types of collagen, such as type I-III collagen. DDR1 is mainly activated by type IV collagen, whereas type V and X collagens interact only with DDR2. Human DDR1 is located on chromosome 6 (6p21.3) between the genes of the major histocompatibility complexes, HLA-E and HLA-C [2]. DDR1 has 17 exons with a coding sequence length of 2742 bp. There are at least 5 isoforms of human and mouse DDR1: the best characterized are DDR1a, DDR1b, DDR1c, DDR1d, and DDR1e [3], which are widely expressed in many tissue types. These isoforms are generated by alternative splicing of mRNA in the catalytic region of the intracellular kinase domain [4]. DDR1a-c has kinase activity, whereas DDR1d and DDR1e lack a kinase domain or have an inactive kinase domain because of premature truncation [5] (Figure 1).

Structural analysis of DDR has shown that it is mainly composed of three regions: the extracellular binding (ECD) domain, the transmembrane (TM) domain, and an intracellular kinase domain. Its structural specificity lies in the presence of a discoidin domain (DS) and a discoidin-like domain in the extracellular domain that can bind to a variety of collagens [6]. The dimerization of DDR1 is an indispensable prerequisite for collagen binding. The TM domain contains two main fragments: an extracellular juxtamembrane region and a TM helix. Phosphorylated tyrosine is present in the extracellular juxtamembrane (JM) region [7]. After the transmembrane domain, there is a large intracellular JM region, a kinase domain, and a short C-terminal tail that regulates ligand-independent dimerization of DDRs and mediate the activation and phosphorylation of downstream signals [8].

DDRs regulate the adhesion and traction of collagen by binding with non-muscle myosin IIA heavy chain (NMHC-IIA), thus concentrating collagen fibers into a denser arrangement [9]. The main binding site for DDR1 and DDR2 is the conserved GVMGFO motif (where O represents hydroxyproline) in type I-III collagen [10]. Different types of collagen are necessary for the activation of DDRs, in which collagen must be in its inherent triple-helix form for binding. When DDR1 combines with collagen, DDR1 dimers form clusters. This enables normal protein molecules in adjacent dimers to phosphorylate each other, initiate signal transduction, and generate a sustained reaction [11]. DDR1 clustering is mediated by ECD and its intracellular domain. Dimerization and higher-order oligomerization of the extracellular domain of DDR1 enhance its binding to collagen

[12].

Unlike other RTKs, collagen binds to DDR1; DDR1 exhibits abnormally slow and persistent autophosphorylation. DDR1 participates in the maximum activation of the receptor within 1-2 h and remains active for 18-24 h [13]. Activation of DDR1 is beneficial for regulating several downstream signaling pathways, such as the PI3K/Akt, JAK/STAT, and MAPK/ERK pathways [14].

The X-ray crystal structure study of the DDR1 kinase domain showed that the DDR1 kinase domain has the same structure as other protein kinases and its ATP-binding site is located in the groove between the two domains. ATP binding sites of kinases can adopt various conformations, and regulatory elements including αC helix and DFG tripeptide are used to classify inhibitors [15]. Based on the conformation of the DFG motif, ATP-competitive inhibitors can be classified into types I and II. Type I inhibitors bind to the active conformation, whereas type II inhibitors bind to the inactive conformation [16].

Regulation mechanism of DDR1 expression

Currently, the mechanism underlying the regulation of DDR1 expression remains unclear. Reportedly, TGF-β1 promotes the up-regulation of smad4-dependent DDR1 and LOXL2 in cultured HCC cells [17]. H-Ras inhibits the expression of the collagen receptor DDR1 through ZEB1, confirming that ZEB1 is a novel transcriptional inhibitor of DDR1 [18]. Endogenous expression of Wnt-5a can induce collagen-induced phosphorylation of DDR1 receptor in breast cancer MCF-7 cells. In MCF-7 cells lacking Wnt-5a, mastoparan-induced G-protein activation phosphorylates DDR1 and enhances its adhesion. Therefore, Wnt-5a and G protein are necessary for DDR1 receptor activation and normal breast cell adhesion [19].

microRNAs (miRNAs) are potent regulators of DDR1 expression. DDR1 is a target gene of mir-199a/b-5p in renal cancer cell lines, and mir-199-a/b 5p regulates the expression of DDR1 [20]. DDR1 is highly expressed in OSCC tissues. Its level is negatively correlated with the expression of miR-486-3p; miR-486-3p reduces the expression of DDR1 by targeting the 3'-UTR of DDR1 mRNA [21].

Increasing evidence has indicated that DDR1 mRNA expression is controlled by epigenetic mechanisms. Treatment of non-small cell lung cancer cell lines with 5-azacitidine can increase the expression of DDR1, suggesting epigenetic regulation of DDR1 [22].

In addition, the expression of DDR1 can be regulated by a shedding mechanism. The activation of DDR1 is partly regulated by the proteolytic activities of membrane-anchored collagenases, MT1, MT2 and MT3-MMP. Shedding of endogenous DDR1 in breast cancer cells is mediated by MT1-MMP, which regulates collagen-induced receptor activation [23]. The broad-spectrum metalloprotease inhibitors GM6001 and Mst can inhibit the shedding of DDR1, which further confirms the role of metalloproteinases. Another study found that ADAM10 is the enzyme responsible for extracellular domain shedding of DDR1 induced by collagen. Extracellular domain shedding is a regulatory mechanism that controls collagen signal transduction and cell migration [24].

The effect of DDR1 on tumor and related signaling pathways

DDR1 is involved in tumor cell differentiation, intercellular adhesion, proliferation, migration, invasion, EMT, apoptosis, and energy metabolism [25], as well as in many signaling pathways (Figure 2).

DDR1 and cell adhesion and epithelial cell differentiation. DDR1 is primarily expressed in epithelial cells and maintains cellular differentiation and tissue homeostasis. DDR1 promotes cell adhesion and differentiation through the stabilization of E-cadherin mediated by Cdc42 inactivation [13]. DDR1 deficiency impairs the adhesion of breast cancer cells, facilitates the expansion of breast basal cells, promotes fibrosis, and enhances necrotic/hypoxic and basal differentiation of transformed cells [26].

DDR1 and extracellular matrix (ECM) and collagen. The ECM in the tumor microenvironment (TME) forms an interconnected network. During tumor development, the ECM is constantly remodeled and new matrix components are synthesized, accompanied by proteolytic degradation. Collagen is the most abundant protein in the ECM. The ECM affects the interaction between collagen and DDRs through a mechanical force signal known as "biomechanical force", which is transmitted by the interaction between extracellular matrix components and integrins [27].

The main collagen receptors in cancer cells are integrins α1β1, α2β1, α10β1, and α11β1. DDRs enhances cell adhesion to collagen mediated by integrins by changing the affinity of α1β1 and α2β1 integrins, but does not affect the surface expression level of α1β1 or α2β1 [28]. Collagen-binding integrins together with DDRs can form a fibrocollagen microenvironment that acts as a trap and

hinders the transport of immune cells to tumor cell clusters [28, 29].

Collagen also binds to cluster of differentiation 44 (CD44) and DDR1 [30]. The interaction between the cytoplasmic domain of DDR1 and cytoskeletal motor proteins may promote remodeling of the ECM by promoting the arrangement and compaction of collagen fibers [27]. In addition, DDR 1 can also bind to periostin, a component of the ECM [31].

In the ECM of the TME, type I collagen shows a high density and is related to tumor invasion. The stromal desmoplastic reaction of pancreatic ductal adenocarcinoma (PDAC) is related to the significant accumulation of type I collagen; a decrease in type I collagen accelerates tumor progression and reduces the survival rate of patients [32]. The interaction between DDR1 and type I collagen plays an important role in this process. DDR1 significantly affects cancer cell metabolism and regulates the regulation of the TME [33].

DDR1 and tumor cell proliferation. DDR1 promotes proliferation of many cancer cells. Inhibition of DDR1 can inhibit the proliferation of non-small cell lung cancer cells, but does not affect the cell cycle or apoptosis [22]. The lipoprotein receptor, LRP1, interacts with DDR1 in colon cancer cells to inducing the endocytosis of DDR1. LRP-1-mediated endocytosis of DDR1 increases cell proliferation by promoting cell cycle entry into the S phase and reducing apoptosis [34]. DDR1 promotes the growth of pancreatic cancer tumors by regulating TGFBI expression. DDR1 knockdown affects the proliferation and migration of tumor cells *in vitro* and their growth *in vivo*. BXPC3 tumor xenografts show growth inhibition after DDR1 knockout [35].

DDR1 and the invasion and metastasis of tumor cells. For tumor cells to invade, they must break through the surrounding basement membrane. This process is crucial for tumor progression, and the migration and invasion abilities of tumor cells are key factors that determine tumor metastasis. Whether DDR1 induces or inhibits cell migration and invasion depends on the environment or expression of cofactors. DDR1 regulates MMP-2 and MMP9; these two enzymes are involved in remodeling and degradation of the basement membrane and play a vital role in tumor invasion [36]. In many types of tumors, cancer cells undergo a period of dormancy after settling at the metastatic site and are reactivated by specific signals to induce metastasis [37]. Researchers have discovered another important function of DDR1 in the process of metastasis; that is, to keep disseminated tumor cells in a dormant state. The dormancy signal of DDR1 depends on its binding to type III collagen but not on its kinase activity. Binding of DDR1 to type III collagen triggers STAT1

activation and nuclear translocation to regulate COL3A1 expression. Increased COL3A1 expression remodels the ECM and drives tumor cells into a dormant state maintained by DDR1 binding [38].

The mechanisms by which DDR1 promotes tumor invasion and metastasis include kinase-dependent and-independent mechanisms depending on the stage of tumor metastasis [39]. DDR1 activates Tuba and Cdc42 in a collagen-rich environment through a kinase-independent mechanism, thus playing an important role in the invasion of breast cancer cells via proteolysis [40]. In addition to its interaction with collagen fibers, DDR1 has other functions that are not dependent on collagen. In A431 cells, DDR1 is recognized in an E-cadherin-dependent manner at the cell/cell junction, where it participates in cell adhesion and collective migration by forming complexes with Par3/Par6 [41]; this function is independent of its collagen-binding and tyrosine kinase activity.

Some studies have shown that the kinase activity of DDR1 plays a key role in tumor invasion and metastasis. The B-cell receptor (BCR) is a novel DDR1 substrate. Nilotinib can prevent DDR1-mediated phosphorylation of BCR at Tyr177 by inhibiting the kinase activity of DDR1 in colon cancer cells, thus participating in the maintenance of tumor cell invasion [42]. The high expression of DDR1 in gastric cancer (GC) cells promotes actin skeleton reorganization by activating HIF-1α/RhoA/ROCK1 signaling pathway, thereby enhancing the metastatic ability [43]. DDR1 expression is significantly increased in breast cancer and is associated with poor patient prognosis [44]. By activating the Src-FAK signaling pathway, DDR1 was positively correlated with enhanced migration and invasion abilities of breast cancer cells. Therefore, blocking the DDR1/Src/FAK axis is a promising therapeutic strategy for breast cancer [44]. Other studies have shown that DDR1 is the main driver of mesenchymal and invasive PDAC phenotypes. DDR1 stimulates the production of CXCL5 through the PKCθ/SYK/NF-κB signaling pathway, thereby promoting the invasion and metastasis of PDAC by forming neutrophil extracellular traps [45].

However, some studies arrived at opposite conclusions. In DDR1-deficient triple-negative breast cancer cell lines, DARPP-32 alone had no effect on cell migration, and the co-expression of DDR1 and its interacting protein, DARPP-32, inhibited tumor cell migration [46].

DDR1 and epithelial to mesenchymal transition (EMT). EMT is a biological process in which epithelial cells lose their polarity and intercellular adhesion and acquire mesenchymal features. EMT is regulated by the expression of epithelial (E-cadherin) and mesenchymal (N-cadherin, vimentin, and MMP9) markers, as well as transcription factors (including Snail1/2, Zeb1/2, and

Twist) [47]. DDR1 regulates the activation of RAS-related protein 1 (RAP1) mediated by PYK2, leading to EMT in pancreatic cancer cells [48]. In GC, overexpression of DDR1 increases the expression of the interstitial markers, vimentin and Snail1, while reducing the expression of the epithelial marker, E-cadherin [49].

ZEB1 is a novel transcriptional inhibitor of DDR1. The role of ZEB1 in maintaining EMT in breast cancer cells is partly mediated by its ability to inhibit the expression of DDR1. ZEB1 can directly interact with the Z-box and E-box elements upstream of the DDR1 transcription initiation site, thereby inhibiting DDR1 promoter activity [18]. PGC1α is a transcription factor involved in energy metabolism and mitochondrial biogenesis. PGC1α leads to the decrease of the expression of known EMT regulatory factors, SNAIL1 and 2, by inhibiting collagen /DDR1 signaling [50].

Some studies have also shown that the expression of DDR1 decreases during EMT. Researchers have found that CpG methylation levels of the DDR1 promoter are negatively correlated with the expression DDR1 in the EMT spectrum. However, DDR1 knockdown did not affect E-cadherin expression [51].

DDR1 and tumor angiogenesis. Tumor neovascularization is essential for the delivery of oxygen and nutrients to promote tumor growth. DDR1 interacts with the PAS domain of hypoxia- inducible factor 1-α (HIF-1α), inhibits its ubiquitination, and significantly promotes angiogenesis, which is a key step in tumor progression. DDR1 inhibition can suppress the progression and angiogenesis of GC in patient-derived xenotransplantation and organoid models [43]. In a nude mouse model *in situ*, angiogenesis and lymphangiogenesis of DDR1-silenced GC cells were significantly reduced, resulting in decreased lymph node and liver metastasis [52]. Epithelial α5 (IV) is crucial for tumor angiogenesis. In lung cancer cells and endothelial cells, the knockdown of DDR1 phenocopied the cells deficient in α5 (IV), thus demonstrating the role of DDR1 in angiogenesis [53].

DDR1 and the immune microenvironment and immune escape. Immune escape is an important characteristic of invasive tumors. Studies have shown that DDR1 promotes tumor immune escape. When DDR1 is functioning, membrane shedding can occur, thereby releasing the entire extracellular domain of DDR1-ECD [2]. The combination of DDR1-ECD and collagen makes the collagen fibers align neatly, causing immune exclusion [54]. Migration of effector T cells through the ECM is an important step in the development of adaptive immune responses and inflammatory diseases. DDR1 promotes the migration of effector T cells through the collagen of perivascular

tissues by activating the RhoA/ROCK/MAPK/ERK signaling axis [55].

Bioinformatic analysis revealed that the expression of DDR1 was negatively correlated with the ratio of CD8+ and CD4+ T cells in anti-tumor immune cells. Animal experiments have further confirmed that HNRNPC and VIRMA enhance the TFAP2A/DDR1 axis, reduce the infiltration of antitumor immune cells, and promote the immune escape of breast cancer [56]. The level of DDR1 negatively correlated with immune infiltration in GC and significantly correlated with various immune cell markers. DDR1 is involved in the immune infiltration and escape of GC, mainly related to CD8+ T cells, macrophages, and dendritic cells [57].

M2 macrophages have the ability to promote tumor growth and inhibit anti-tumor immune response, and provide immune escape microenvironment for tumor cells by secreting various immunosuppressive factors, such as TGF-β and IL-10. The DDR1 signaling pathway promotes the polarization of tumor-associated macrophages (TAMs) to the M2 phenotype, thus promoting immune escape and ovarian cancer progression [58].

However, some studies have shown that the inhibition of DDR1 may induce a pro-tumor TME. In the KRAS/ p53-driven lung adenocarcinoma immune mouse model, tumors with DDR1 knockout showed a reduction in CD8+ cytotoxic T cells and an increase in CD4+ helper and regulatory T cells [59].

DDR1 and autophagy. Autophagy is a process by which cells degrade and recycle proteins and organelles to maintain intracellular homeostasis [60]. DDR1 and 14-3-3-Beclin-1-Akt1 protein complexes are involved in Akt and mTOR signal transduction in glioblastoma and the regulation of autophagy-related therapeutic sensitivity [61]. Thus, DDR1 may be a potential target for glioblastoma cells to be sensitive to combination therapy by effectively inducing autophagic cell death [62].

DDR1 and ferroptosis. Ferroptosis is a form of RCD induced by iron-dependent lipid peroxidation, and promotes tumor cell death. Studies have shown that with an increase in the concentration of the ferroptosis inducer, erastin, the expression of DDR1 in bladder cancer cells gradually decreased, while the expression of DDR1 in anti-ferroptosis BC cells was not affected. DDR1 inhibits ferroptosis by regulating the expression of HOXA6, thereby promoting bladder cancer [63].

DDR1 and metabolic reprogramming. Metabolic remodeling is one of the most obvious tumor characteristics. During tumor progression and drug resistance, malignant cells respond to various

extracellular and endogenous signals to meet higher metabolic demands. This phenomenon is called "metabolic remodeling" or "metabolic reprogramming" [64]. Insulin receptor isomer A (IR-A) is a dual receptor for insulin and IGF2. DDR1 silencing induces a decrease in the mitochondrial ATP production rate in breast cancer cells overexpressing IGF2 or IR-A, as well as the downregulation of key molecules involved in glycolysis and oxidative phosphorylation [65]. Extracellular acidification rate, oxygen consumption rate, and lactic acid production were used to determine the effect of DDR1a on metabolic reprogramming. Results showed that DDR1 promoted the proliferation of LoVo cells, mitochondrial function, and extracellular acidification, and played a vital role in maintaining homeostasis of the intracellular environment by regulating metabolic reprogramming [66].

The Role of DDR1 and other signaling pathways in tumor progression. Ngai et al. have demonstrated that DDR1 and the YAP/PDZ-binding motif (TAZ) form a mechanically sensitive positive feedback loop. DDR1 controls the nuclear localization and activity of YAP/TAZ, and YAP/TAZ mediates DDR1 expression by promoting DDR1 transcription [67]. DDR1 is phosphorylated in a p53-dependent manner in response to DNA damage. Subsequently, the Ras/Raf/MAPK and AKT pathways are triggered, resulting in increased levels of p53, phosphoserine-15, p53, p21, ARF, and Bcl-X(L). These signaling effects improve the survival rate of cancer cells under genotoxic stress [14]. In breast cancer, DDR1 binds to collagen, thereby recruiting tetraspanin, TM4SF1. TM4SF1 couples DDR1 with cortical adaptor syntenin 2, and then with PKCα. PKCα phosphorylates and activates JAK2, which leads to the activation of STAT3, thus causing the metastatic reactivation of lung, bone, and brain, and maintaining tumor stem cell characteristics [68]. Overexpression of the IR plays a recognized role in cancer progression and resistance to anticancer therapy. DDR1 not only interacts with IR-A, but is also an insulin-like growth factor 1 receptor (IGF-1R)-interacting protein, which positively regulates the expression and biological response of IGF-1R, thereby suggesting that DDR1-IGF-IR crosstalk may play an important role in breast cancer progression [69].

DDR1 mediates chemotherapy resistance

Chemotherapy resistance in tumor cells is one of the main reasons for treatment failure. Studies have shown that DDR1 is involved in chemotherapy resistance (Figure 3). In mouse embryonic

fibroblasts, DDR1 activates the NF-KB pathway to induce the expression of cyclooxygenase-2 and promote chemotherapy resistance [70]. DDR1 causes therapeutic resistance in stem cell-like cells and somatic cells of glioblastoma multiforme (GBM) through adhesion to the ECM and subsequent macrophage/autophagy regulation [62]. DDR1 knockdown can significantly enhance the sensitivity of ovarian cancer cell lines to cisplatin and promote apoptosis [71]. In a study of platinum-based drugs for the treatment of KRAS-mutant lung cancer, high DDR1 expression during chemotherapy was associated with adverse reactions to chemotherapy in patients with lung cancer. Moreover, drug inhibition of DDR1 produces a synergistic therapeutic effect with chemotherapy [72].

The presence of DDR1/2 also reduces the sensitivity of wild-type or primary KIT mutants to imatinib, indicating that DDR1/2 may promote the survival of gastrointestinal stromal tumor (GIST) during KIT-targeted therapy [73]. DDR1 may also be an important mediator of acquired chemotherapy resistance because acquired mutations and/or chemotherapy induce the selection of preexisting subclone mutations during treatment [74].

In terms of the mechanism by which DDR1 mediates drug resistance, spatial dysregulation of RTKs may promote the development of cancer and affect the sensitivity and resistance of cancer to RTK inhibitors [75]. Moreover, DDR1 interacts with other signaling pathways that have pro-survival effects, further increasing the complexity of drug resistance mechanisms. DDR1 also functionally interacts with cytokines, such as integrin and transforming growth factor β (TGF-β). Integrin not only helps to activate the survival pathway but also affects drug response and chemotherapy resistance [76]. Elevated TGF-β levels are associated with chemotherapy resistance and poor prognosis of cancer.

Therapeutic strategy of targeting DDR1

Considering the important role of DDR1 in tumor cell proliferation, adhesion, and migration, as well as in subsequent tumor metastasis and drug resistance, many studies have shown that targeting the expression or signal transduction of DDR1 may be an effective strategy to inhibit tumor metastasis and recurrence. Therefore, DDR1 is a promising target to overcome treatment resistance and develop more effective treatment strategies. Based on this, researchers worldwide are making great efforts to develop selective DDR1 inhibitors and have made considerable progress. For example, the small-molecule chemical ICP-033, produced by Beijing Nuocheng Jianhua

Pharmaceutical Technology Co. Ltd., has undergone Phase I clinical trials [77].

DDR1 inhibitors can be divided into three categories: monoclonal antibodies, small-molecule inhibitors, and antibody-drug conjugates (ADCs) [78]. As the kinase domains of DDR1 and DDR2 have high sequence and structural homology with those of c-Kit and Bcr-Abl kinases, many DDR1/2 inhibitors also exert inhibitory effects on these kinases [79].

Antibody. Neutralizing antibodies against DDR1 have been developed that can disrupt the tumor barrier, promote infiltration of immune cells, and enhance the antitumor immune response [54]. Zhong et al. found increased expression level of DDR1 in human breast tumors and that the overexpression of DDR1 in mouse breast cancer 4T1 cells can promote tumor growth, whereas the use of DDR1 neutralizing antibody can reduce the growth of breast cancer *in vivo* [80]. As DDR1 clustering plays a crucial role in the phosphorylation of DDR1 dimers, some researchers have developed new drugs targeting DDR1 clustering that may help treat cancers, inflammation, and fibrosis caused by abnormal DDR activity. Researchers have developed a monoclonal antibody, 3E3, that inhibits DDR1 signaling without interfering with collagen binding. This antibody binds to DDR1 ECD, effectively blocking the extracellular association of DDR1 subunits and inhibiting collagen-induced receptor phosphorylation [81], as well as DDR1 clustering [11].

Another study developed a monoclonal antibody, PRTH-101, against DDR1. PRTH-101 interacts with the discoid protein-like domain of DDR1 but not with the collagen-bound DS domain. PRTH-101 inhibits the phosphorylation of DDR1, reduces collagen-mediated cell adhesion, and significantly prevents the shedding of DDR1 from the cell surface, thereby disrupting the arrangement of collagen fibers, alleviating immune exclusion, and inhibiting tumor growth in the host [82].

Small-molecule inhibitors. Small-molecule inhibitors block downstream signal transduction by inhibiting the kinase activity of DDR1 and are classified as non-selective kinase inhibitors and selective kinase inhibitors. Currently, most DDRs inhibitors are competitive ATP inhibitors that either bind to the active conformation of DDRs (type I inhibitor) or the inactive conformation of DDRs (type II inhibitor), preventing the transfer of the terminal phosphate group of ATP to the protein substrate [83]. The most selective DDR1 inhibitors are type II kinase inhibitors, which bind to the DFG conformation.

Nonselective kinase inhibitors. Owing to the structural similarity of the kinase domain (KD), most

Bcr-Abl inhibitors such as dasatinib, nilotinib, and imatinib can inhibit DDR1 [84] (Table 1). Nilotinib reverses the TME dominated by neutrophils/NETs and effectively enhanced the response of HCC to PD-1 [85]. Flow cytometry analysis revealed that nilotinib significantly induce the death of apoptotic breast cancer cells and effectively block the migration of breast cancer cells [86]. Dasatinib can inhibit key kinases (SRC, FRK, DDR1, and SIK2) that are highly expressed in patients with GC, thereby inhibiting proliferation of GC and playing a therapeutic role in GC [87]. The combination of DDR1/2 inhibitors and imatinib, the first-line targeted therapy for GIST, can significantly inhibit tumor growth [73]. However, at present, there is still a lack of selectivity for RTK inhibitors that target DDR1, resulting in poor therapeutic and off-target effects. Furthermore, the mechanism underlying the relationship between DDR1 and the disease is not yet comprehensive, resulting in a lack of conclusive evidence for the clinical indications of DDR1 inhibitors [29]. Therefore, it is of great importance to develop small-molecule inhibitors that specifically target DDR1.

Selective Inhibitors. Single-target inhibitors. Because DDR1 is highly homologous to many other human kinases, the development of selective DDR1 inhibitors is challenging. With in-depth research on DDR1, specific DDR1 inhibitors have been developed (Table 2, Figure 4). DDR1 inhibitors must contain basic pharmacophores such as hinge-binding regions, spacers, linkers, and tails. In the hinge-binding region, different heterocyclic skeletons such as pyrazine, quinazoline, pyrimidine, fused pyrimidine, thiazole, indazole, pyrarole, or pyridine can be added [1].

Preliminary biological evaluations conducted by the National Cancer Institute of the United States have shown that KST9046 has a strong inhibitory effect on 60 tumor cell lines and exhibits high selectivity and broad-spectrum antiproliferative activity against DDR1. Elkamhawy et al. proposed that KST9046 is a noncompetitive inhibitor that acts on DDR1 through ATP-binding sites, based on molecular docking studies [88]. The DDR1 inhibitor, 7rh benzamide, inhibited tumor growth in GC xenografts [89]. Moreover, compound 7rh has demonstrated antitumor activity in nasopharyngeal carcinoma cells, either alone or in combination with dasatinib, an inhibitor of SRC family kinase (SFK) [90].

Mo et al. studied a predictive model and identified chemical characteristics that could control the efficacy and selectivity. And a series of 3'-(imidazo[1,2-a]pyrazin-3-yl)-[1,1'-biphenyl]-3-carboxamides with high specificity for DDR1

were discovered. Compound 8v dose-dependently inhibits the carcinogenicity, migration, and invasion of non-small cell lung cancer cells [91]. Romayer et al. found that the secretion of colon cancer can increase the phosphorylation of DDR1 in hepatic stellate cells, while inhibiting DDR1 with DDR1-IN-1 can reduce the expression of chemokines and proliferation factors and decrease liver metastasis in mouse models [92]. Researchers have designed and synthesized a series of 2-amino-2, 3-dihydro-1h-indene-5-carboxamides as new DDR1 inhibitors. Among them, 7f is representative, which can inhibit the formation of pancreatic cancer cell colonies in a dose-dependent manner and shows good therapeutic effect *in vivo* in a mouse model of pancreatic cancer *in situ* [93]. Liu et al. developed a series of novel indole-urea derivatives as effective inhibitors of DDR1. Among them, compound 7s has the strongest inhibitory effect on lung adenocarcinoma A549 cells (IC50: 1.84 μM), and compared with that of dasatinib, compound 7s exhibits stronger anti-tumor activity [94].

In addition to the traditional DDR1 inhibitors mentioned above, the exploration of new inhibitors targeting the interaction between DDR1 and its interacting molecules is underway. The combination of DDR1 inhibitors with other drugs has promising application prospects. Owing to the interaction and synergistic effects of DDR1 and integrins in tumors, targeting both DDR1 and integrin molecules simultaneously has potential for the treatment of cancer and fibrosis. The combination of the selective DDR1 kinase inhibitor, DDR1-IN-1, and cilengitide, which inhibits integrin αVβ3/αVβ5, can reduce the clonal formation ability of GBM cells and improve the radiotherapy effect [95]. Aguilera et al. found that collagen activates DDR1 through PYK2 and PEAK1 kinase-mediated tumor-promoting signaling pathways, and the use of 7rh to inhibit DDR1 in combination with chemotherapy has shown high efficacy in an orthotopic xenograft model of PDAC [96].

Double-target inhibitor. Recently, a series of innovative double-target inhibitors targeting DDR1 and other molecules have been developed. D06 exhibits micromolar enzymatic activity against DDR1 and EGFR. In the xenograft model of PC-9/GR for non-small cell lung cancer, D06 demonstrated good anti-tumor activity without obvious toxicity [97]. Researchers have designed and optimized a series of dual DDR1/2 inhibitors, heterocycloalkynylbenzimides, in which compound 5n had a significant anti-inflammatory effect in a mouse model of LPS-induced acute lung injury [98]. Compound 3j, as a novel dasatinib analog, demonstrated superior inhibitory

efficacy against both DDR1 and DDR2 compared to the parental dasatinib and also showed effective inhibitory activity against the K562 cell line [84]. Other dual DDR1/DDR2 inhibitors have also been reported one after another [99, 100]. These results demonstrated the successful synthesis of effective dual-target inhibitors and their promising application prospects in disease treatment. Compared to single-target drugs, multi-target drugs have shown better efficacy in treating diseases with complex pathogenesis [101].

Combined therapy. The combination of DDR1 inhibitors and chemotherapy is expected to treat various cancers. In future research, combination therapies should be explored, especially the combined use of DDR1 inhibitors with immunotherapy and targeted drugs, to enhance efficacy and overcome drug resistance.

Antibody-drug conjugates. ADCs combine the powerful antitumor efficacy of small molecule drugs (300-1,000 Daltons) with the high selectivity, stability, and good pharmacokinetic properties of monoclonal antibodies [102]. ADCs are increasingly used in clinical treatments, including first-line cancer treatment. Researchers have developed an ADC drug, T4 H11-DM4, which targets DDR1. T4 H11-DM4 demonstrated strong antiproliferative activity in colon cancer cell lines *in vitro*. In safety studies, T4H11-DM4 was administered at a single dose of 50 mg/kg to BALB/c mice or at multiple doses of 10 mg/kg to BALB/c nude mice; however, no significant toxicity was observed [103].

The current challenges faced by DDR1 inhibitors

DDR1 is involved in different stages of tumor development and metastasis, and has become a promising therapeutic target in oncology. The application of DDR1 inhibitors in an increasing number of preclinical cancer models suggests a promising future for discoid domain kinase inhibitors.

However, the following situations need to be seriously considered: i) DDR1 is crucial for the normal development of physiological processes; for instance, DDR1 and its ligand, collagen IV, are involved in the maturation of oligodendrocytes *in vitro* [104]. DDR1 plays a significant role in lung development. A deficiency of DDR1 can induce pulmonary hypertension and impair alveolar development [105]. Therefore, when developing inhibitors of DDR1, the impact on the biological functions of DDR1 should be considered to avoid potential side effects. ii) The role of DDR1 in

different cancer types may vary, requiring in-depth research for each cancer type. iii) It cannot be ignored that problems such as poor selectivity and drug resistance of DDR1 inhibitors still exist. Moreover, owing to an incomplete understanding of the pathological mechanisms of DDR1, most new and effective DDR1 inhibitors are only used as tools for pharmacological research. iv) Another complexity in targeting DDR1 is that it has five isoforms. To develop specific inhibitors, it is necessary to gain a better understanding of the functions and molecular pathways of these isoforms [5]. v) As members of the receptor tyrosine kinase family, although both DDD1 and DDR2 receptors are expressed in many tissues and play a role in cancer, few studies are currently available that have investigated the effects of DDR1 and DDR2 in the same cancer. Therefore, future studies should consider whether DDR2 compensates for DDR1 inhibitors.

Conclusion and prospect

Given the current problems of DDR1 inhibitors, developing dual-target (such as simultaneously targeting DDR1 and DDR2) or multi-target inhibitors might be a promising new strategy in future research. In addition to DDR1 kinase inhibitors, alternative methods, such as allosteric modulators, protein degradants, and therapeutic antibodies, are expected to become the focus of this field. Proteolytic-targeted chimeras (PROTACs) are a novel concept in drug development [106]. Future studies should confirm whether PROTACs can induce degradation of the intracellular and extracellular components of DDR1, which will help eliminate receptor kinases in tumor therapy. The extracellular domain of DDR1 can inhibit the infiltration of immune cells and promote tumor growth, making DDR1 a potential new target for immunotherapy. With further research, new drugs targeting DDR1 will show great value and broad application prospects in cancer treatment.

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Figure Legends

Figure 1. Subtypes and structures of discoid domain receptor 1 (DDR1).

Figure 2. DDR1-related signaling pathways and their functions in cancer progression.

Figure 3. The role of DDR1 in cancer progression.

Figure 4. The chemical structures of the small molecule inhibitor of DDR1.

819 **Table 1.** Non-selective kinase inhibitors of DDR1.

Inhibitor	Target	Category	Tumor	Functions	Ref.
Nilotinib	DDR1	Type-II	Breast cancer	Induces the death of apoptotic breast cancer cells and blocks the migration	[86]
Dasatinib	DDR1, DDR2	Type-I	Gastric cancer	Inhibits proliferation of GC	[87]
Imatinib	BCR-ABL, DDR1, DDR2	Type-II	GIST	Inhibits the growth of GIST	[73]

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822 **Table 2.** Selective kinase inhibitors and antibody-drug conjugates of DDR1.

Inhibitor	Heterocyclic scaffold/Category	Cell lines	Functions	Ref.
KST9046	Quinazoline-urea	60 tumor cell lines	A strong inhibitory effect	[88]
7rh benzamide	Pyrazole fused pyrimidine	Gastric cancer, nasopharyngeal carcinoma	Inhibits tumor growth	[89, 90]
Compound 8v	Imidazole fused pyrazine	Non-small cell lung cancer	Inhibits the carcinogenicity, migration, and invasion	[91]
DDR1-IN-1	Pyrrole fused pyrimidine	Colon cancer	Reduces the expression of chemokines and proliferation factors	[92]
Compound 7f	Indene fused carboxamide	Pancreatic cancer	Inhibits the formation of cell colonies	[93]
Compound 7s	Indole-urea derivatives	Lung adenocarcinoma	Anti-tumor activity	[94]
D06	Pyrimidine diamine	Non-small cell lung cancer	Anti-tumor activity	[97]
Compound 3j	Imidazole fused pyrazine	Chronic myeloid leukemia	Inhibits tumor growth	[84]
T4H11-DM4	Antibody-drug conjugates	Colon cancer	Antiproliferative activity	[103]

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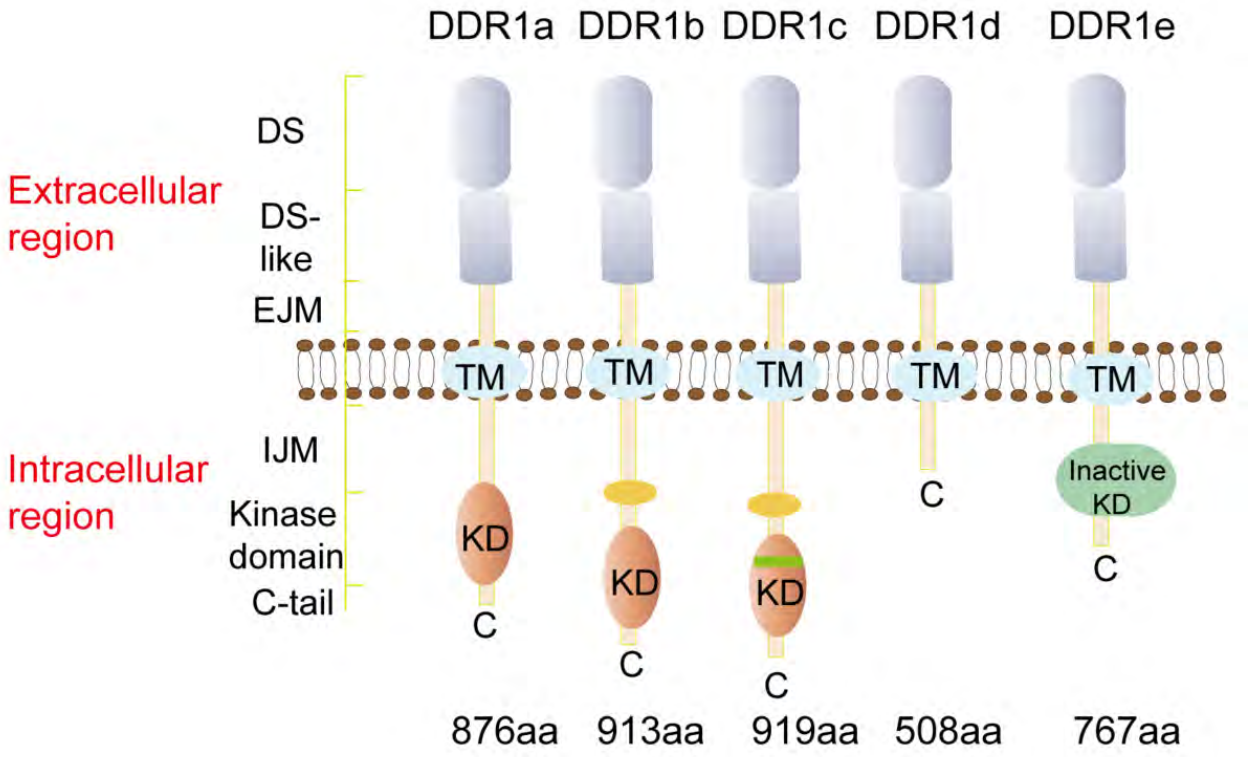

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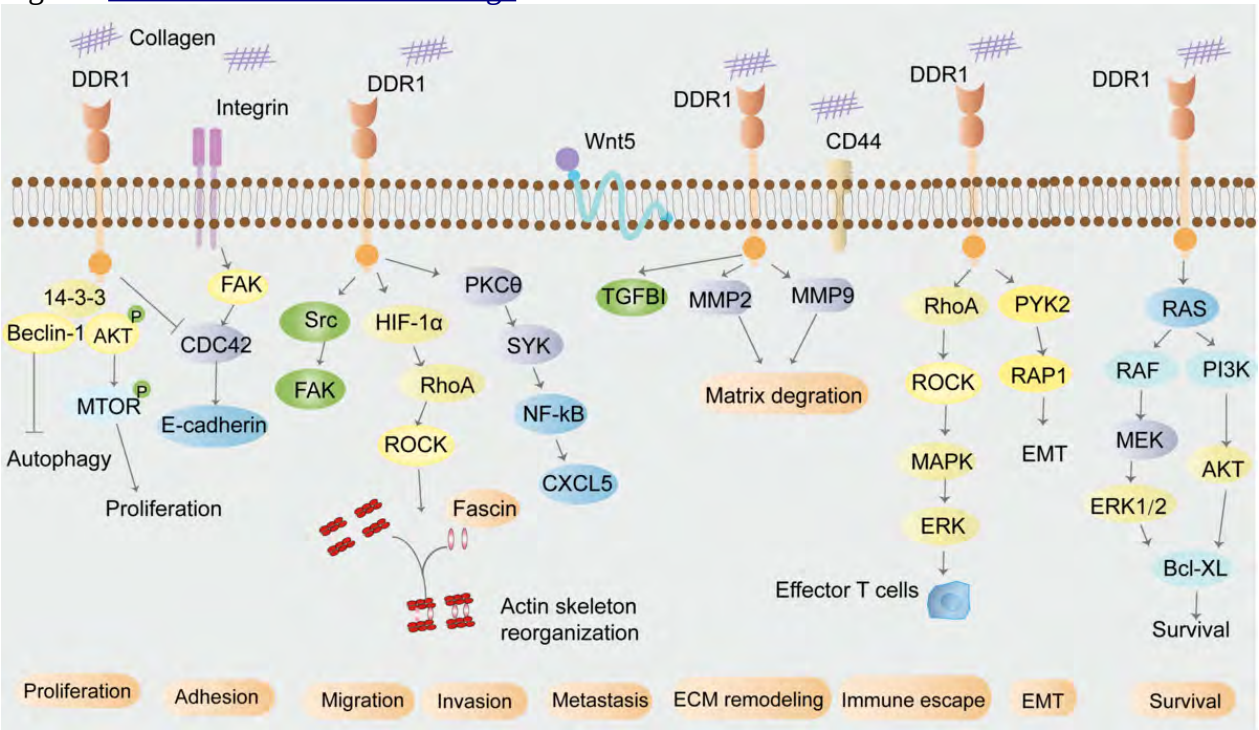

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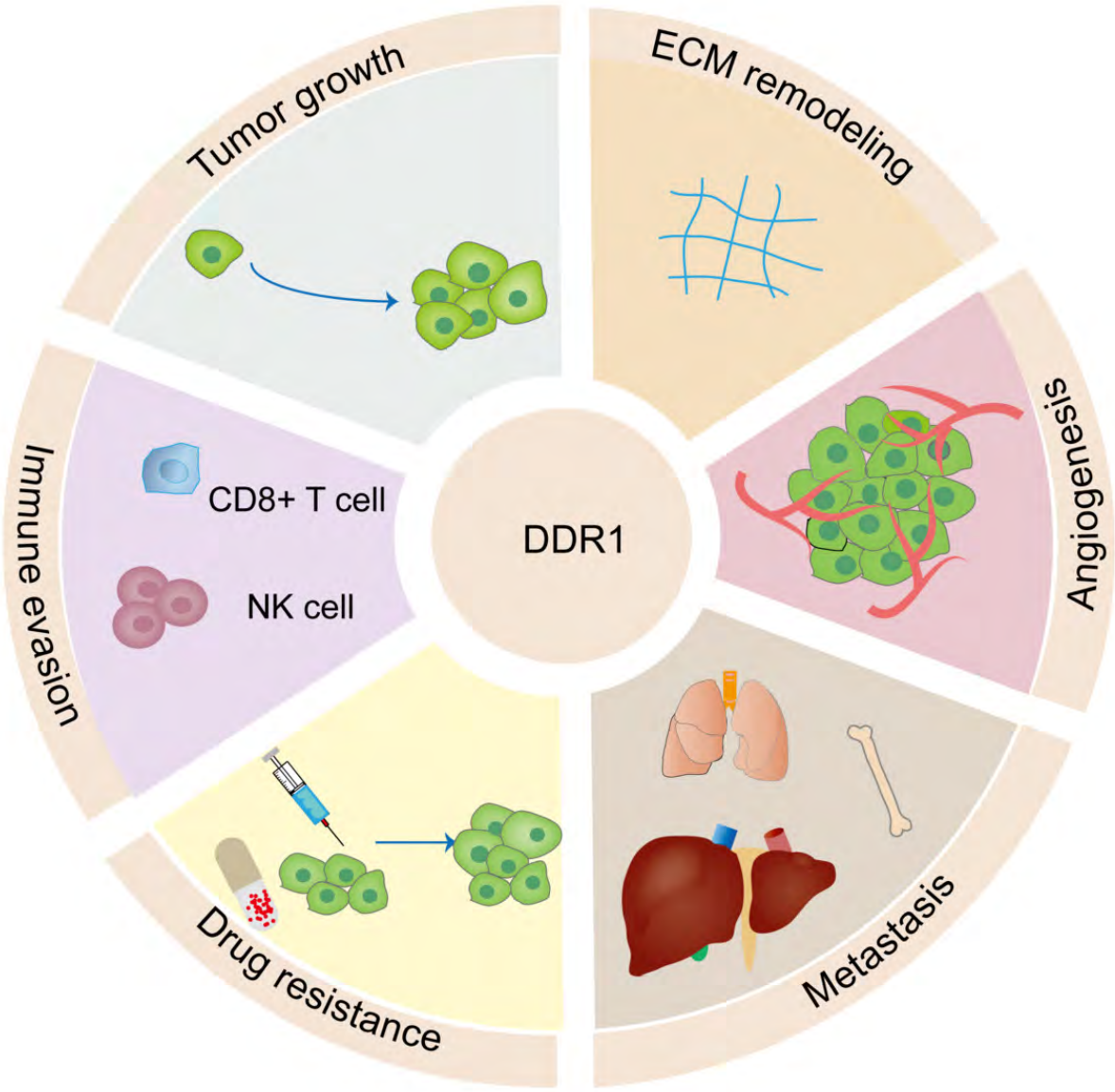

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