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Discoidin domain receptors orchestrate cancer progression: A focus on cancer therapies

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Abstract

Discoidin domain receptors (DDR), including DDR1 and DDR2, are special types of the transmembrane receptor tyrosine kinase superfamily. DDR are activated by binding to the triple-helical collagen and, in turn, DDR can activate signal transduction pathways that regulate cell-collagen interactions involved in multiple physiological and pathological processes such as cell proliferation, migration, apoptosis, and cytokine secretion. Recently, DDR have been found to contribute to various diseases, including cancer. In addition, aberrant expressions of DDR have been reported in various human cancers, which indicates that DDR1 and DDR2 could be new targets for cancer treatment. Considerable effort has been made to design DDR inhibitors and several molecules have shown therapeutic effects in pre–clinical models. In this article, we review the recent literature on the role of DDR in cancer progression, the development status of DDR inhibitors, and the clinical potential of targeting DDR in cancer therapies.

KEYWORDS

antagonists and inhibitors, discoidin domain receptors, neoplasms, receptor protein-tyrosine kinases, therapeutic uses

1 | INTRODUCTION

Discoidin domain receptors (DDR), including DDR1 (CD167a) and DDR2 (CD167b), are special types of transmembrane (TM) receptor tyrosine kinases (RTK) discovered in recent years.[1] Unlike typical RTK, the ligands of which are peptide-like growth factors, DDR1 and DDR2 are activated by binding to collagen, which are the most abundant proteins in the extracellular matrix. DDR1 and DDR2 play key roles in the regulation of collagen production and degradation, which is a distinctive feature of DDR.[2,3] Interestingly, Vella et al (2019) found that DDR activation can also be mediated by the insulin/insulin-like growth factor receptor (IIGFR) system, which does not require collagen binding.[4]

Collective evidence suggests that expression of DDR1 and DDR2 differs. DDR1 is widely expressed in epithelial cells, while DDR2 is mainly found in mesenchymal cells.[5,6] DDR are essential for the homeostasis of multiple organs. Thus, the disruptive expression will lead to organ dysfunction or carcinogenesis.[7] Indeed, both DDR1 and DDR2 are overexpressed in many cancer types and are related to disease progression as well as poor prognosis.[8-10]

Because DDR are key players in cancer, exploration of DDR inhibitors is urgently needed. Because of the similarity of the kinase domain (KD) structure, many recognized tyrosine kinase inhibitors, such as the BCR-ABL inhibitors nilotinib and dasatinib, can effectively inhibit the kinase activity of DDR1 or DDR2.[8,11] However, these inhibitors are non–selective, which limits further research

on the inhibitive effects of specific DDR.[12] Since 2013, the development of new DDR1 inhibitors, such as pyrazolopyrimidine derivatives, monoclonal antibodies, and artificial intelligence (AI)-generated DDR1 inhibitors, has increased rapidly, which indicates that DDR inhibition may represent a novel therapeutic strategy.[13-15]

In this article, we review the basic structural characteristics and functions of DDR, the role of DDR in tumorigenesis, and the recent development of DDR inhibitors, aiming to provide new insights into anti–DDR therapy for cancer patients.

2 | STRUCTURAL CHARACTERISTICS, SUBTYPES, AND ACTIVATION OF DISCOIDIN DOMAIN RECEPTORS

Like other RTK, the molecular structure of DDR contains three parts: the extracellular binding domain, the TM domain, and the intracellular KD.[7,12] The extracellular binding domain is composed of a discoidin (DS) domain and a DS-like domain for collagen binding. The TM domain is composed of an extracellular juxtamembrane (JM) region, containing phosphorylatable tyrosines, that serves as a docking site for DDR binding proteins, and a TM helix that mediates collagen-independent receptor dimerization.[16] The intracellular domain contains an intracellular JM region and a catalytic tyrosine KD,[17]which determines the intrinsic enzymatic activity.[10,18] Collagen binding can promote tyrosine kinase Src to phosphorylate tyrosines in the DDR activation loop.[17] Subsequently, the activation of KD in DDR is believed to autophosphorylate various additional tyrosines in the JM region, which then recruit downstream adaptor proteins to regulate cell behavior.[19,20]

DDR1 has five isoforms, including DDR1a-e, while DDR2 only has one isoform.[19] The differences between these isoforms are caused by the alternative splicing of mRNA in the catalytic region of the intracellular KD.[21] Among all subtypes of DDR1, DDR1d and DDR1e are kinase-deficient due to the lack of a complete reading frame (Figure 1).[22]

Unlike other RTK, DDR are activated by different types of collagen instead of soluble growth factors.[17] Typical RTK activation is

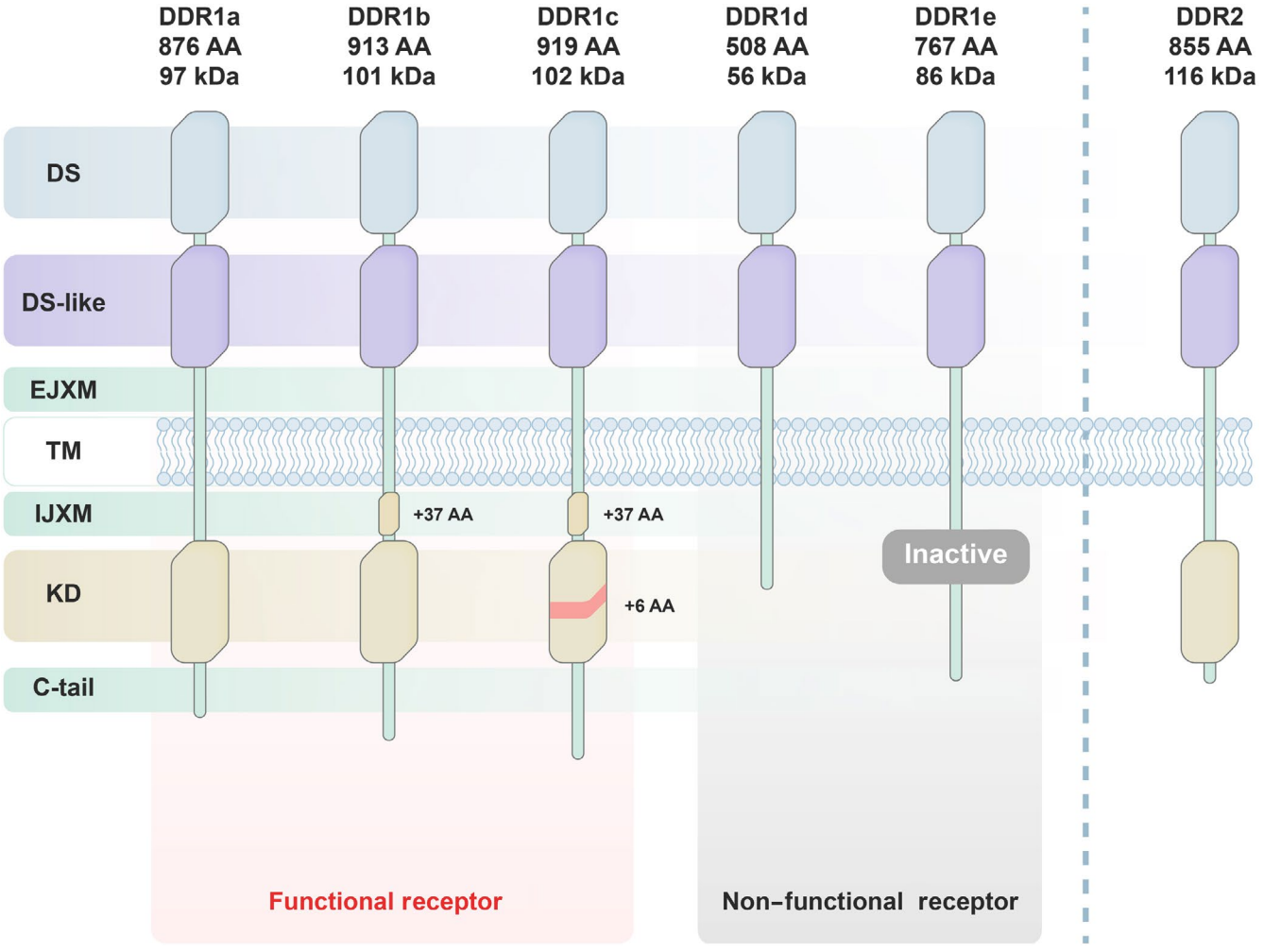

FIGURE 1 Structures and subtypes of DDR1 and DDR2. DDR1a, b, and c are kinase-active, while DDR1d and e are kinase domain-deficient. AA, amino acid; DS, discoidin domain; DS-like, discoidin-like domain; EJXM, extracellular juxtamembrane region; IJXM, intracellular juxtamembrane region; KD, kinase domain; TM, transmembrane segment

triggered within a few seconds after binding to a ligand.[23] However, the phosphorylation process of DDR is remarkably slow, taking several hours to achieve full activation.[17,21] Previously, it was thought that DDR could only be activated by collagen binding. In recent years, researchers have found a novel activation model of DDR by interaction with the IIGF system.[3] Insulin, IGF1, and IGF2 can upregulate DDR1 expression and induce its phosphorylation in a collagen-independent manner. In turn, DDR1 expression enhances the activity of IR and IGF1R, which indicates that the IIGF-DDR1 crosstalk is positive feed-forward.[24] Further studies need to be conducted to illustrate the regulatory mechanisms between DDR and IIGF.

3 | DISTRIBUTIONS AND BIOLOGICAL FUNCTIONS OF DISCOIDIN DOMAIN RECEPTORS

Discoidin domain receptors are widely expressed in human tissues and are crucial for the regulation of organ development and physiological function.[23] As collagen sensors, DDR are not only involved in the process of cell proliferation and differentiation but are also related to the process of cell migration, invasion, and adhension.[5,25]

DDR1 and DDR2 play an important role in the biogenesis of multiple organs. Mice with *Ddr1*-knockout showed multiple reproductive disorders, including infertility due to abnormal implantation of the embryo and abnormal development of the mammary glands.[26] As for DDR2, Labrador et al[27] found that the *Ddr2*^{slie}/^{slie} mice developed skeletal disorders such as shortening of long bones and irregular growth of flat bones. *Ddr2*-knockout mice displayed skin wound-healing disorders, which were mainly related to suppressed skin fibroblast proliferation, and extracellular matrix remodeling abnormalities.[28]

There are limited reports of DDR having immunomodulatory functions. One study provided evidence that DDR1 mediated activated T cells to bind to collagen, which enhanced T cell migration.[29] In addition, the combination of DDR1a and collagen can promote migration of leukocytes to participate in host defense.[30] Zhong et al[31] revealed that DDR1 regulated triple-negative breast cancer growth by modulating tumor infiltrating CD4+ and CD8+ T cells. Tu et al[32] reported an in vivo study using isogenic mice models that showed that DDR2 reduction increased the population of CD8+ T cells and sensitivity to anti–programmed cell death protein 1 (PD-1) treatment. However, the specific regulation mechanisms and whether DDR affect other immune checkpoints remain unclear.

4 | DISCOIDIN DOMAIN RECEPTORS IN CANCER

DDR1 and DDR2 are activated in various pathological processes. Based on studies in pre–clinical models and clinical specimens, it has been suggested that DDR are closely related to many human

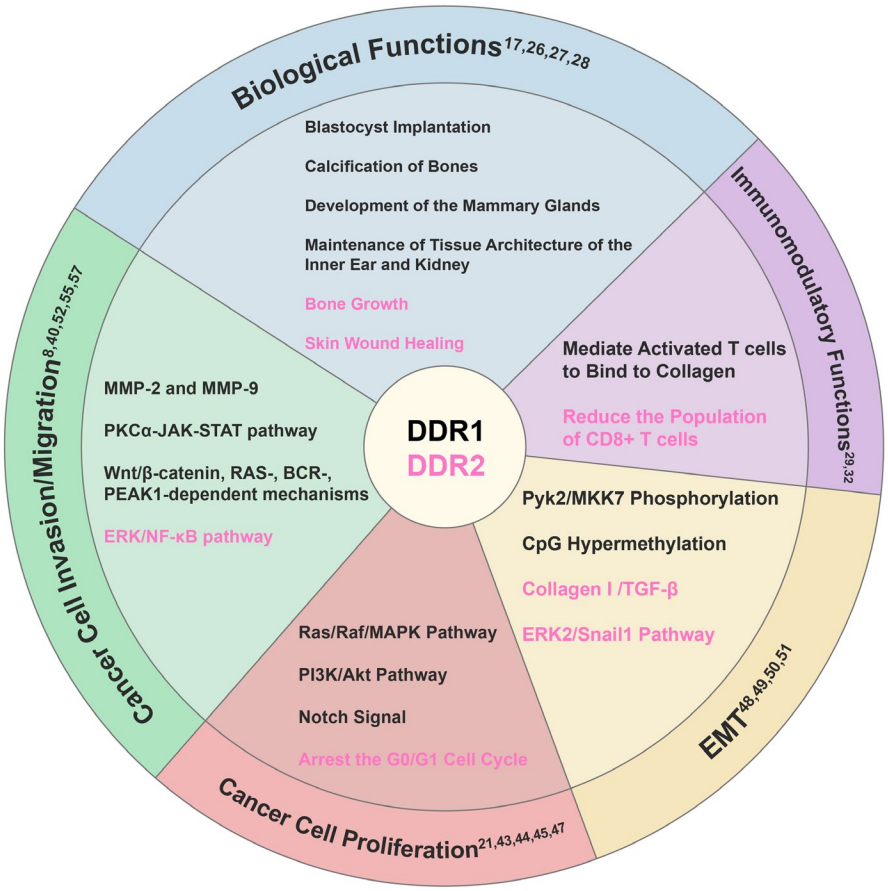

FIGURE 2 Regulatory mechanisms of DDR1/DDR2 in biological development, immunomodulation, cancer cell proliferation, invasion/migration and epithelial to mesenchymal transition

malignancies.[8,33] It appears that the role of DDR depends on the type and stage of the cancer, although DDR affect the biological behavior of tumor cells by activating different signal pathways (Figure 2).[34]

5 | EXPRESSION AND MUTATIONS OF DISCOIDIN DOMAIN RECEPTORS IN HUMAN CANCERS

Studies indicate that DDR1 or DDR2 overexpression has a positive correlation with poor prognosis of cancer patients.[10] For example, DDR1 and DDR2 are highly expressed in invasive ductal breast cancer,[35] and the expression levels of DDR1 and DDR2 are significantly related to advanced TNM stage and lymph node metastasis.[36] Moreover, in an immunohistochemical analysis of 171 cases of non–small cell lung cancer (NSCLC), the positive rate of DDR1 in aggressive NSCLC was as high as 61%.[37] In a study of esophageal squamous cell carcinoma (SCC), Sugimoto et al.[38] showed that the expression levels of DDR1 and phosphorylated-DDR1 were higher in invasive esophageal SCC compared with normal adjacent tissues and were negatively related to patient survival. Several studies have demonstrated that the expression level of DDR2 is related to tumor stage, lymph node metastasis, and poor prognosis in colorectal cancer (CRC) patients.[39,40] In contrast, some studies have found that DDR1 acts as a tumor suppressor. For instance, Takai et al[36] found that *DDR1*$^{-/-}$ tumors are more aggressive than controls in a luminal-type breast cancer mouse model. Thus, the role of DDR in breast cancer is controversial and further studies are needed.

Dysregulation of DDR in cancers may be caused by somatic mutations. A recent publication found that the *L63V* mutation of *DDR2* could induce poorly differentiated lung adenocarcinoma in a *Tp53*$^{L/L}$ mice model.[41] In estrogen receptor-positive breast cancer, the R776W mutation of DDR1 is highly associated with poor prognosis in patients treated with tamoxifen.[42] Overall, these studies suggest that DDR mutations can contribute to cancer formation and likely act as new oncogenic biomarkers.

6 | CELL PROLIFERATION AND SURVIVAL

In vitro and in vivo studies have shown that DDR are involved in tumor cell proliferation. In breast cancer, colon carcinoma, and osteosarcoma cell lines, DDR1 promotes cell survival through the Ras/Raf/mitogen-activated protein kinase pathways under genotoxic stress.[43] In KRAS-mutated lung cancer, DDR1 facilitates lung cancer cell proliferation by activating the phosphatidylinositol 3-kinase/protein kinase B signaling pathways.[21,44] In colon cancer cells, DDR1 can activate Notch 1 to upregulate the expression of pro–survival genes *Hes1* and *Hey2*.[45] Meanwhile, overexpression of DDR2 induced by cyclooxygenase-2 can promote proliferation of U2OS human osteosarcoma cells.[46] These data indicate that DDR can promote tumor cell proliferation, although there is also a study showing that DDR2 can inhibit cell growth in fibrosarcoma by arresting the G0/G1 cell cycle.[47] Potential reasons for the different effects of DDR may be specific to cell type or cancer type.

7 | EPITHELIAL TO MESENCHYMAL TRANSITION

Many studies have confirmed that DDR are related to epithelial to mesenchymal transition (EMT) in a ligand-type and cell-type dependent manner.[17] For example, DDR1 activation can induce phosphorylation of proline-rich tyrosine kinase 2 and map kinase kinase 7 (Pyk2/MKK7), which promotes the EMT in prostate cancer cells.[48] In epithelial ovarian cancer, loss of DDR1 can induce EMT through CpG hypermethylation at its promoter.[49] In breast cancer, collagen I-activated DDR2 can stimulate ERK2/SNAIL1 signaling to promote EMT.[50] In A549 lung carcinoma cells, DDR1-knockdown and DDR2-knockdown can suppress collagen I or transforming growth factor-beta (TGF-β)-induced EMT.[51] All these studies show that DDR can promote EMT through interactions with different downstream signaling pathways depending on cell types.

8 | CELL MIGRATION

In breast cancer cells, DDR1 interacts with tetraspanin transmembrane 4 L six family 1 (TM4SF1) to regulate tumor metastasis through activation of the PKCα-JAK-STAT signaling pathway.[52] Researchers have proposed that in CRC, DDR1 supports the metastatic process through Wnt/β-catenin-dependent, RAS-independent,[40] as well as BCR-dependent and PEAK1-dependent mechanisms.[8] Other studies show that DDR can express suppression ability in cell migration. For example, DARPP-32 is a dopamine and cAMP-regulated neuronal phosphoprotein with molecular mass 32 kDa, which was originally identified in dopaminergic nerve terminals. In the DDR1-deficient breast cancer cell line MDA-MB-231, DARPP-32 alone has no effect on cell migration, while co–expression of both DDR1 and DARPP-32 can suppress cell migration.[53] However, the downstream effectors or signal pathways involved in regulating DDR1 function in cell migration need to be further explored.

9 | CELL INVASION

Tumor cell invasion is a process that requires extracellular matrix degradation and tissue remodeling. MMP is a class of extracellular matrix degrading enzymes that is important for tumor cell invasion.[54] In MDA-MB-231 breast cancer cells, DDR1 induced invasion through upregulation of MMP-2 and MMP-9 secretion.[55] Studies have also found that overexpression of DDR1 can induce invasion of colon carcinoma cells through upregulation of MMP-2.[56] For DDR2, a recent study demonstrated that DDR2 inhibition can decrease invasion of B16BL6 melanoma cells by suppressing MMP-2

and MMP-9 expression via the ERK/NF-κB pathway.[57] However, researchers showed that downregulated DDR2 in mouse B16-F10 melanoma cells had no effect on lung metastasis.[34] Thus, further studies are required to clarify the precise molecular mechanisms of DDR in cell invasion in different cancers.

10 | DISCOIDIN DOMAIN RECEPTOR INHIBITORS

Because DDR may become potential targets for cancer treatment, the development of DDR inhibitors is flourishing. Most current DDR inhibitors are competitive ATP inhibitors. They either bind to the active (type-I inhibitor) or the inactive conformation (type II inhibitor) of DDR and block the terminal phosphate group of ATP transfer to the protein substrate.[58] Recently, the type-III DDR inhibitor, which targets the allosteric site but not the ATP binding site to regulate kinase activation, has also been generated.[59]

Due to the structural similarity of the KD, many recognized BCR-ABL tyrosine kinase inhibitors, such as imatinib (type II) and dasatinib (type I), have been found to have an inhibitory effect on DDR.[58] Imatinib is a non–selective DDR1 inhibitor that simultaneously inhibits both DDR1 (half maximal inhibitory concentration [IC_{50}] value = 337±56 nmol/L) and DDR2 (IC_{50} value = 675±127 nmol/L).[60] Dasatinib is a multi–kinase RTK inhibitor that can inhibit the activity of DDR1 at a very low concentration (IC_{50} value = 3.7 ± 1.2 nmol/L).[58] Interestingly, the combination of dasatinib and anti–PD-1 antibody decreased the tumor burden synergistically in an MC38 colon cancer mouse model and a 1956 sarcoma mouse model.[32] We speculate that the combination of DDR inhibitors with immune checkpoint inhibitors may achieve improved therapeutic effects.

In recent years, many new selective DDR inhibitors have been generated. For example, researchers designed a series of type II inhibitors, such as DDR1-IN-1 and DDR1-IN-2,[61] that can effectively inhibit phosphorylation of DDR1, with IC_{50} values of 105 nmol/L and 47 nmol/L, respectively.[58]

Moreover, pyrazolopyrimidine derivatives (**7rh** and **7rj**) and tetrahydroisoquinoline derivatives (compound **10**) can selectively inhibit the activity of DDR1 with high affinities.[62,63] In addition, benzamide derivatives, such as compounds **23** and **24**, exhibit inhibitory abilities against DDR1, with IC_{50} values of 97 nmol/L and 43 nmol/L, respectively, and their anti–tumor effects have been confirmed in in vivo experiments.[64,65] Mo et al (2020) investigated a highly selective DDR1 inhibitor compound **8v**. This inhibitor is a 3′-(imidazo[1,2-a] pyrazin-3-yl)-[1,1′-biphenyl]-3-carboxamide and inhibits DDR1 with an IC_{50} of 23.8 nmol/L. In addition, functional studies showed that compound **8v** suppressed the proliferation and adhesion of NSCLC cells.[15]

Due to the high specificity, mAb are thought to be promising inhibitors against DDR.[66] For instance, DDR1 mAb 48B3 can prevent the invasion and adhesion of G140 human glioma cells.[67] In 2019, Tao et al[68] developed a DDR1 antibody DM4 (an anti–tubulin agent blocking cell division) drug conjugate called T4H11-DM4, which can suppress colon cancer tumorigenesis in vitro and in vivo.

Artificial intelligence-designed DDR1 inhibitors have also been explored. One study reported a DDR1-targeted inhibitor using a machine learning approach called generative tensorial reinforcement learning (GENTRL).[66] Through running GENTRL with the known

TABLE 1 Activities and categories of DDR inhibitors

Target	Inhibitor	IC_{50} DDR1	IC_{50} DDR2	Category
Multi-targeted kinase inhibitors	Imatinib[58]	337 ± 56.0 nmol/L	675.0 ± 127.0 nmol/L	Type-II
	Nilotinib[7]	43.0 ± 3.0 nmol/L	55.0 ± 9.0 nmol/L	Type-II
	Dasatinib[56]	0.5 ± 0.2 nmol/L	1.4 ± 0.3 nmol/L	Type-I
ATP site kinase inhibitors	DDR1-IN-1[59]	105.0 nmol/L	413.0 nmol/L	Type-II
	DDR1-IN-2[59]	47.0 nmol/L	147.0 nmol/L	Type-II
Small molecular DDR inhibitors	**7rh**[60]	6.8 nmol/L	101.4 nmol/L	Pyrazolopyrimidine derivatives
	7rj[60]	7.0 nmol/L	93.6 nmol/L	Pyrazolopyrimidine derivatives
	Compound **10**[61]	9.4 nmol/L	—	tetrahydroisoquinoline derivatives
	Compound **8v**[14]	23.8 nmol/L	—	3′-(imidazo[1,2-a] pyrazin-3-yl)-[1,1′-biphenyl]-3-carboxamide
	Compound **23**[63]	97.0 nmol/L	—	Benzamide derivatives
	Compound **24**[63]	43.0 nmol/L	—	Benzamide derivatives
DDR1 antibodies	48B3[65]	20 μg/mL	—	Monoclonal antibody
	T4H11-DM4[66]	2.5 nM (HT-29) 22.1 nmol/L (HCT116) >1 μmol/L (LoVo)	—	Antibody-drug conjugate
AI-designed DDR1 inhibitors	Compound 1[13]	10.0 nmol/L	—	AI-designed

The bold types are inherent in the references.

Abbreviations: "-", not available; AI, artificial intelligence; ATP, adenosine triphosphate; DDR, discoidin domain receptor.

DDR1 inhibitors and common kinase inhibitors in the database, researchers obtained 30 000 structures for DDR1 inhibitors and, finally, chose six structures to synthesize the molecules. After biological evaluation, compound 1 was considered the most potent DDR1 inhibitor, with the IC_{50} value of 10 nmol/L (Table 1).[14]

11 | CONCLUDING REMARKS AND PERSPECTIVES

DDR1 and DDR2 are emerging as attractive targets and biomarkers in oncology as they play a key role in cancer progression at multiple levels.[10,33] Although the physiological and pathological functions of DDR have been widely reported, detailed molecular mechanisms remain to be elucidated. For example, conflicting data exist on the oncogenic function of DDR1 in breast cancer.[69] Therefore, understanding the specific cell characteristics that DDR rely on to provoke oncogenesis is critical. Although DDR are not frequently mutated, examining the function of specific mutations will help in the selection of target patients and may improve the therapeutic efficacy. Recent work has shown a role for DDR in regulating the immune response,[31,32] so identifying whether and how DDR increase susceptibility to immunotherapy will be essential.

Various DDR inhibitors with different mechanisms of action have been studied and some of them exhibit therapeutic potential for human cancers.[14] However, the search for more specific DDR inhibitors continues because the large inhibitory profiles could lead to poor tolerability of patients. In addition, evidence shows that DDR2 inhibition enhances anti–PD-1 efficacy, suggesting a rationale for a combination of DDR inhibitors and anti–PD-1 therapy.[32] Thus, more data are required to examine whether this combination is tolerable and efficient for improved tumor control.

In summary, DDR are emerging as novel and attractive regulators of cancer progression and the development of selective DDR1 or DDR2 inhibitors is of great significance. We look forward to a detailed portrayal of the role of DDR and the arrival of DDR inhibitors into the clinical armamentarium to achieve encouraging results with cancer therapies.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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