Review Article

Roles of discoidin domain receptor 1 in gastrointestinal tumors

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Abstract: Discoidin domain receptors (DDRs) are receptor tyrosine kinases that recognize collagens as their ligands and are expressed in both epithelium and mesenchyme cells. DDR1 and DDR2 are two unique members of the DDRs family. Recent studies have demonstrated that DDR1 is closely associated with the proliferation, invasion, immigration, and epithelial-mesenchymal transformation (EMT) of solid tumor cells. Inhibiting the DDR1 activity can effectively suppress tumor growth by activating a variety of factors and signaling pathways. Novel selective DDR1 inhibitors may be promising strategies for cancer treatment. This article reviews the roles of DDR1 in gastrointestinal tumors.

Keywords: Discoidin domain receptor 1 (DDR1); receptor tyrosine kinase; gastrointestinal Tumor

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Discoidin domain receptors (DDRs) are discovered receptor tyrosine kinases composed of extracellular discoidal homologous domains in recent years. These receptors sustained receptor phosphorylation upon binding to collagen (1-3). DDRs are significantly associated with cell morphology, proliferation, differentiation, adhesion, migratory, and invasive processes (4,5). DDR expressions have been found in the early stages of embryonic development. In mice, the deficiency of DDR is related to bone development, inflammation, reproduction, and cardiovascular functions (6-9). DDRs are characterized by 4 different domains: N-terminal discoidin (DS) domain and a DS-like domain which binds to collagen. According to the different sequence homologies in the C-terminal region, DDRs are divided into DDR1 and DDR2, among which DDR1 has 5 subtypes, while DDR2 has only 1 subtype. Each of these five DDR1 subtypes plays different roles such as glycosylation, phosphorylation, and protein interactions (10,11). DDR1 and DDR2 share high degree of sequence identity in DS and DS-like domains. DDRs are the only tyrosine kinases that can be phosphorylated by various collagens. DDR1 can be activated by collagen types I–VI and VIII, whereas DDR2 uses only collagen type I and III as its ligands (11-13). DDR1 is expressed in various epithelial cells such as lung epithelium, intestinal mucosal epithelium, ovary, breast, and thyroid follicular epithelium (14,15). In contrast, DDR2 is mainly expressed in interstitial cells (4). DDRs are associated with a variety of cellular functions such as cell proliferation, migration, adhesion, and changes in an extracellular matrix structure. DDRs are dysfunctional in cells in a variety of diseases (3,16). High expression of DDR1 has been found in breast cancer, gastric cancer (GC), pancreatic cancer, lung cancer, and colorectal cancer (CRC) cells, and its expression level is associated with tumor progression (17-20). Activation of DDR1 can regulate cell proliferation, invasion, and metastasis by affecting the signaling pathways in tumor cells (21,22), whereas inhibition of DDR1 activity can suppress tumor

progression. Thus, DDR1 may become a new therapeutic target in the treatment of gastrointestinal (GI) tumors and increase the sensitivity of tumor cells to chemotherapy. Therefore, targeting DDR1 may become a new strategy for cancer treatment.

Roles of DDR1 in the proliferation, invasion, and migration of GI tumors

Role of DDR1 in GC

As one of the most common malignant GI tumors, GC is characterized by low early diagnostic rate, high degree of malignance, and early metastasis (23). Research has found that DDR1 is expressed in GC cell lines, and high expression level is related with poor prognosis. In the *in vitro* experiment, DDR1 was highly expressed in GC cell lines (BGC825, SGC7901, and MKN45); after transfection with DDR1-siRNA, the proliferation of GC cells was significantly suppressed, and the ability of migration and invasion were significantly lower as compared with the control group; furthermore, DDR1 overexpression promoted BGC825 cell migration and invasion (24). DDR1-silenced MKN74 cells showed unaltered proliferation activity. In contrast, migration, invasion, and tube formation were significantly reduced. In nude mice model with the transplantation tumor, DDR1-silenced implanted tumors significantly reduced angiogenesis and lymphangiogenesis, thereby leading to reductions in lymph node metastasis and liver metastasis (25). Similar results were obtained in human tumors. Xie *et al.* (24) detected the expression of DDR1 in tumor tissues from 160 GC patients by immunohistochemistry and found that its expression was significantly higher in GC having poor differentiation, advanced depth of wall invasion, lymph node metastasis, and liver metastasis; they also concluded that DDR1 enhances invasion and metastasis of GC via epithelial-mesenchymal transformation (EMT). Hur *et al.* collected 202 gastric carcinoma specimens and found that over half of GC tissues were positive for DDR1 expression (18). Positive DDR1 expression was significantly correlated with poor prognosis: DDR1 expression was detected in 58.8% of stages T3 and T4 primary GC tissue, showing a significant difference (P=0.017), and DDR1-positive patients had significantly shorter overall survival (OS) (P=0.015). However, they did not find any correlation between the DDR1 expression and the differentiation and lymphatic metastasis of GC. Finally, the authors observed that oral administration of a DDR1 inhibitor, 7rh, suppressed tumor growth in GC xenografts.

Role of DDR1 in CRC

CRC is one of the most commonly malignancy-related deaths in China. The role of DDR1 in CRC development has also been described. Hu *et al.* (20) found that, compared with the adjacent tissues, CRC tissues showed a significant increase in mRNA and protein expression levels of DDR1. LOVE1 and LOVO colon cancer cell lines with positive DDR1 expression were transfected with DDR1-shRNA for colony formation assay, which revealed that both the colony formation and the invasive and migratory capabilities of cells were remarkably reduced in the transfection group. Flow cytometry also showed that inhibition of DDR1 expression induced G1 phase arrest and reduced the proportion of cells entering S phase, eventually suppressing cell proliferation (20). Also, in HCT116 cells expressing DDR1, DDR1 inhibited tumor cell apoptosis and promotes cell survival through the Notch1 pathway (26). In *in vitro* experiment, shRNAs strongly inhibited the invasive abilities of *KRAS*-mutated HCT116 and *BRAF*-mutated HT29 CRC cell line. The migratory capability of HCT116 cells in nude mouse models was significantly suppressed; overexpression of DDR1 increased the invasive capability of *KRAS*-mutant SW620 cells as well as liver metastasis development (27). Nilotinib, a tyrosine kinase inhibitor, inhibits the DDR1-regulated invasion and metastasis capabilities of CRC cells in a RAS-dependent manner (28).

Role of DDR1 in pancreatic ductal carcinoma (PDC)

As a common malignant tumor, PDC has a worse prognosis than many other tumors due to its orthotopic implantation and distant metastasis in early stage and its poor response to radiotherapy, chemotherapy, and targeted molecular therapy (29-33). DDR1 overexpression has been detected in PDC. DDR1 binds to collagen and activates FAK-associated protein kinase, thus promoting N-cadherin expression. DDR1 and N-cadherin expressions can be found in primary PDC and its hepatic metastases (34). Also, the binding of transmembrane-4-L-six-family-1 (TM4SF1) expressed in PDC cells to DDR1 can promote invadopodia formation and cell migration and induce the expressions of metalloproteinases 2 and 9, results in degradation of the extracellular matrix (35,36). TM4SF1 is expressed in a

variety of pancreatic cancer cells and can promote tumor cell metastasis; studies have demonstrated that cell invasion and migration are associated with the up-regulation of DDR1 expression (35). To investigate the relationship between DDR1 and PDC, Huo *et al.* (37) carried out a study in 205 Chinese PDC patients, among whom 126 patients had DDR1 mRNA and protein expressions, which were significantly higher in tumor tissues than in adjacent tissues. DDR1 expression was negatively correlated with prognosis, and OS was significantly longer in patients with low DDR1 mRNA and protein expressions (P=0.013) (37). In xenograft and genetically engineered mouse models, oral administration of a small-molecule kinase inhibitor (7rh) effectively inhibited DDR1, decreased tumor burden, and improved chemotherapy response (38). Collagen I activates JNK1 signaling pathway through DDR1, thus inducing EMT in pancreatic cancer (39).

In summary, DDR1 can promote the survival of GI tumors, and its expression is correlated with poor prognosis. DDR1 may promote tumor proliferation and metastasis through mechanisms such as Notch pathway, N-cadherin, and EMT. However, due to the small sample sizes and other study limitations, the correlations of DDR1 expression with malignant tumor features such as poor differentiation, lymph node metastasis, and distant metastasis remain controversial.

Mechanisms of DDR1 in tumor progression

Many recent studies have confirmed that DDR1 acts as a carcinogenic factor in various tumors and plays a role in promoting tumor growth, invasion, and metastasis. However, the mechanism of action of DDR1 in GI tumors remains unclear. Some of these explanations involve the activation of multiple factors and signaling pathways. It has been proposed that DDR1 is associated with the p53 and Notch pathways. As a transcriptional targeting gene of the tumor suppressor p53, DDR1 can be activated or phosphorylated in a p53-dependent manner (40). Inhibition of DDR1 can increase the apoptosis of wild-type p53 tumor cells. DDR1 can also activate the Notch pathway in a p53-independent manner to regulate cell proliferation (40). In colon cancer cells, DDR1 promotes tumor cell survival also in a way associated with the Notch pathway (26). The expressions of β-cadherin-related target genes including *JUN*, *FOSL1*, *CD44*, *MYC*, *CCND1*, *LGR5*, and *AXIN2* were increased upon DDR1 activation, which play key roles in regulating the migration and stem cell-like characteristics of CRC cells (27). The circ-NSD2/miR-199b-5p/DDR1/JAG1 axis also plays an important role in the metastasis of CRC (41). Therefore, it is believed that the ability of DDR1 in maintaining the migration, regeneration, and survival of tumor cells is related to the carcinogenic activity of β-cadherin. Nilotinib inhibits DDR1 activity in CRC cells via a Ras-dependent pathway, thus suppressing tumor metastasis (28). Also, DDR1 acts synergistically with other pathway receptors (e.g., Wnt5a/Frizzled and Notch1 receptors) in HCT116 tumor cells to exert its anti-cancer activity (26). In pancreatic cancer cells, DDR1 promotes cell migration partially by down-regulating TGF-β1 (42). In hepatoma cells, the TGF-β1-dependent regulation of DDR1 expression is associated with the Smad4 signaling pathway (22). Other studies have also found that LMP1, NF-κB, and some other pathways have a positive correlation with the regulatory effect of DDR1 on tumors (22,43,44). The mechanisms of action of DDR1 in GI tumors are complex. Multiple signaling pathways or factors are involved in the process of DDR1 promoted proliferation and invasion in GI tumor. Therefore, further study on the role of DDR1 in different tumors helps us to investigate the mechanisms via which DDR1 regulates these tumors.

Advances of DDR1 inhibitors in cancer treatment

Many studies have demonstrated that overexpression of DDR1 can promote tumor proliferation, invasion, and metastasis, whereas down-regulating DDR1 expression and inhibiting DDR1 activity suppress tumor proliferation, invasion, and metastasis. Therefore, targeting DDR1 may be a new strategy in treating DDR1-positive tumors. Imatinib, dasatinib, nilotinib, and bafetinib, which were originally used to inhibit Abelson (Abl) kinase activity, can inhibit DDR1 activity and thus to suppress the proliferation of DDR1-positive tumor cells (45-47). Since these novel inhibitors were originally used to inhibit Abl kinase activity, they are not selective for DDR1. The novel DDR1 inhibitors (DDR1-IN-1 and DDR1-IN-2) can selectively inhibit the activity of DDR1 and play a role in inhibiting cell proliferation in a variety of tumor cell lines (48). The 7rh compound of 3-(2-(pyrazolo[1,5-a] pyrimidin-6-yl) ethynyl)benzamide is a novel selective inhibitor of DDR1 and is currently under development in preclinical studies. In lung cancer mice carrying a Kas mutation, oral administration of 7rh significantly reduced tumor size, as assessed by computed tomography (CT) (49); significant reduction of the total tumor burden was observed

after oral administration of 7rh in nude mice with GC xenografts (18); also, 7rh could enhance the responsiveness of GC cell lines to 5-FU.

In summary, DDR1 inhibitors can inhibit tumors *in vitro* and nude mouse models, although more studies are warranted before the clinical use of these drugs. Highly selective DDR1 inhibitors can better inhibit tumor progression and reduce toxicities.

Conclusions and prospects

DDR1 is a member of the receptor tyrosine family and is expressed in a variety of tumors such as breast cancer, lung cancer, CRC, and GC. DDR1 has a specific correlation with the proliferation, invasion, and metastasis of tumor cells. Patients with high DDR1 expression have a shorter OS and worse prognosis. Few studies have explored DDR1, and the mechanism of action of DDR1 in tumors remains controversial. Further studies on the mechanisms via which DDR1 promotes tumor progression and exert its roles in cell signaling pathways will guide the use of DDR1 in the diagnosis, treatment, and prognostic prediction of tumors. Targeting DDR1 may become a new strategy for cancer treatment.

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Footnote

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