

Discoidin domain receptor 1: New star in cancer-targeted therapy and its complex role in breast carcinoma (Review)

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Abstract. Discoidin domain receptor 1 (DDR1) is a receptor tyrosine kinase activated by various types of collagens that performs a critical role in cell attachment, migration, survival and proliferation. The functions of DDR1 in various types of tumor have been studied extensively. However, in breast carcinoma, the roles of collagen-evoked DDR1 remain ill defined. Although a number of studies have reported that DDR1 promotes apoptosis and inhibits migration in breast carcinoma, it has also been reported to be associated with tumor cell survival, chemoresistance to genotoxic drugs and the facilitation of invasion. The present review summarizes current progress and the complex effects of DDR1 in the field of breast carcinoma, and presents DDR1 as a promising therapeutic target.

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1. Introduction

Discoidin domain receptors (DDR) are receptor tyrosine kinases (RTKs) characterized by an ~155 amino acid extracellular discoidin homology domain that binds to and is activated by collagens in their native triple-helical form. There are two types of DDR kinases: DDR1 and DDR2. DDR1 is activated by collagens type I-VI and VIII, whereas DDR2 is activated by fibrillar collagens type I and III (1-3). Alternative splicing generates five DDR1 isoforms: DDR1a, DDR1b, DDR1c, DDR1d and DDR1e. DDR1a, DDR1b and DDR1c are full-length functional receptors, whereas DDR1d and DDR1e are truncated and kinase-inactive receptors (4). DDR1 signaling is required for differentiation, immune response, normal skeletal development, mammary gland branching morphogenesis, migration and wound healing (5). The expression of DDR1 in several different types of human cancer, including breast cancer, renal clear cell carcinoma, non-small cell lung carcinoma, esophageal cancer, astrocytoma, prostate cancer, hepatocellular carcinoma and Hodgkin's lymphoma, suggests a function in tumor progression (6-14).

Breast carcinoma is the most common type of malignancy in women, with 1.7 million new cases diagnosed worldwide in 2012 (15). Collagens are a major component of the extracellular matrix (ECM); increasing evidence has demonstrated that collagen performs a critical role in the development and progression of breast carcinoma (13,14). In normal breast tissues, if fibrillar collagen deposition is increased, high mammographic density will be detected; it leads to a 2-fold increased risk of breast carcinoma development (16,17). Therefore, DDR1 may serve an important role in breast carcinoma. In renal clear cell carcinoma and a number of other types of cancer, DDR1 was significantly overexpressed in high-grade and advanced-stage tumors (6,12), suggesting that it may be suitable for use as a prognostic marker or therapeutic target. However, in breast carcinoma, the expression of DDR1 and the stage of the cancer do not appear to be associated (18). Different expression levels of DDR1 may be a reflection of its complex effects in breast carcinoma. This review summarizes the current knowledge regarding DDR1 and discusses its complex effects in breast carcinoma.

2. Collagen-induced DDR1 activation

DDRs are unique among RTKs as they are activated by collagen, an ECM protein. Collagens are major components

of the ECM, accounting for ~30% of the total protein mass in the human body (19). Evidence has demonstrated that high mammographic density, which is partly due to increased fibrillar collagen deposition, is associated with a 2-fold increased risk of breast cancer development (16,17). The native triple-helical collagen serves as a ligand of DDR1; DDR1 cannot be activated by heat-denatured collagen (20,21). DDR1 is activated by specific types of collagens, as aforementioned. The DDR collagen-binding sites are entirely contained within the discoidin 1 domains (1-3). Leitinger *et al* (21) demonstrated that the isolated discoidin 1 domains of DDR1 and DDR2 bind directly to collagen with high affinity and that binding requires these domains to be dimerized. Initial mutagenesis experiments mapped the collagen-binding sites to three spatially adjacent surface-exposed loops that are highly conserved between the DDRs (21,22). DDR1 and DDR2 bind the GVMGVO (O, hydroxyproline) motif within fibrillar collagens I-III (23-25). Analysis revealed that the activation of DDR1 by collagen results in the binding of CD9 to Tyr513, SH2-domain containing protein to Tyr703, 796 and 740, and the p85 subunit of phosphoinositide 3-kinase to Tyr881 (20,26-28). These interactions were confirmed and additional binding proteins, including Ras GTPase activating protein, SH-2 domain-containing inositol 5' polyphosphatase (SHIP)1, SHIP2, signal transducer and activator of transcription and SRC family kinases, were identified using proteomics approaches (29). Therefore, following binding to collagen, DDR1 becomes phosphorylated at tyrosine residues and can activate various downstream signaling pathways.

3. DDR1 expression level in breast carcinoma

Studies with large sets of clinical follow-up data and patients have been performed to verify the DDR1 expression profiles of different histological types of breast carcinoma (Table I). Invasive ductal and lobular carcinomas are the most common histological types of breast carcinoma (30,31). DDR1 was identified to be differentially expressed between lobular and ductal carcinomas by a pairwise comparison analysis (32). DDR1 was overexpressed in ductal carcinomas, as confirmed by immunohistochemistry, in which DDR1 was positive in 96.2% of ductal carcinomas compared with only 13.8% of lobular carcinomas (33). Considering this, DDR1 may represent a novel tissue marker in the differentiation of ductal and lobular breast carcinoma as an addition to the well-established marker E-cadherin (32-34). In triple-negative breast carcinoma, a DDR1^{low}/DDR2^{high} subtype has been identified that may be more invasive and associated with a worse prognosis (13). In human breast cancer stem cells with the CD44^{high}CD24^{low} phenotype, DDR1 expression was reduced (35-37). In other histological types of breast carcinoma, the expression level of DDR1 is lower in the more mesenchymal and invasive Basal B type cell lines, a subtype with enhanced invasive properties (38). Overall, the DDR1 expression profiles of different histological types of breast carcinoma may vary, as summarized in Table I.

4. DDR1 association with EMT in breast carcinoma

The epithelial-to-mesenchymal transition (EMT) program promotes cell motility, invasion and metastasis (39-41).

Table I. Expression levels of DDR1 in different types of breast carcinoma.

Breast cancer type	DDR1 expression	
	High	Low
Metastasis-containing lymph nodes	(83)	
Ductal carcinoma <i>in situ</i>	(13,84)	
Invasive ductal carcinoma	(32,48,85)	
Invasive lobular carcinoma		(32,84,85)
Middle to high-grade carcinoma		(54)
Triple-negative breast carcinoma		(13,84)

DDR1, discoidin domain receptor 1.

EMT is characterized by an increase in cell motility, invasiveness and stem cell-like properties. Tumor cells that undergo EMT express fewer epithelial markers, including E-cadherin and cytokeratins, but express more mesenchymal markers, including vimentin and N-cadherin, with a possible switch in DDR expression from DDR1 (epithelial) to DDR2 (mesenchymal) (42,43). DDR1, as opposed to DDR2, is down-regulated to induce the expression of the EMT transcription factors Twist and Snail in breast epithelial cells, suggesting a differential regulation of DDRs during the development of EMT (2,44,45). In breast carcinoma cells, DDR1 negatively regulates EMT. DDR1 is expressed predominantly in regions of cell-cell contact, where it interacts with and stabilizes E-cadherin in normal epithelial cells (46-49). Studies on tissue samples of patients with breast cancer also demonstrate a negative correlation between DDR1 and zinc finger E-box-binding homeobox 1 (ZEB1) expression. ZEB1 is a key regulator of the EMT program in human breast cancer cells and can directly suppress the transcription of E-cadherin to promote EMT (33). Therefore, when the expression level of DDR1 is high, it may inhibit ZEB1 and the EMT program. Furthermore, the overexpression of DDR1a or DDR1b reduces the invasive phenotype and regulates the F-actin cytoskeletal organization of breast cancer cells (46). Therefore, in breast cancer cells, DDR1 serves a negative function in the EMT program.

5. Complex role of DDR1 in migration

Studies have demonstrated that DDR1 functions in the regulation of cell adhesion and migration in tumors (50-53). Neuhaus *et al* (54) used chemokine-driven transwell migration assays to assess the migration of small interfering RNA (siRNA)-transfected cells and detected a marked reduction of cell migration following the knockdown of DDR1 in T47D and MDA-MB-468 breast cancer cell lines; T47D cell migration was reduced by 23% and MDA-MB-468 migration by 57%. It was concluded that when DDR1 is downregulated, the migration ability is also decreased. A study has demonstrated that DDR1 can mediate cell migration by means of regulating the migration suppressor Syk kinase (55), providing further evidence for a pro-migratory role of DDR1. Castro-Sanchez *et al* (56) demonstrated that in MDA-MB-231

Table II. *In vitro* functions of discoidin domain receptor 1 in breast carcinoma progression.

Process	Positive regulator	Negative regulator
Proliferation/survival	MCF-7 (78) MDA-MB-435 and T47D (80)	MCF-7 and ZR-75-1 (70,86)
Migration	MCF-7 (57) MDA-MB-231 (58) MDA-MB-468 and T47D (54)	MCF-7 (59) MDA-MB-231 (46,59) Hs578T (46)
Invasion	MDA-MB-231 (58,87)	Not reported
Epithelial-to-mesenchymal transition	Not reported	Hs578T, MCF-7 and MDA-MB-231 (46)

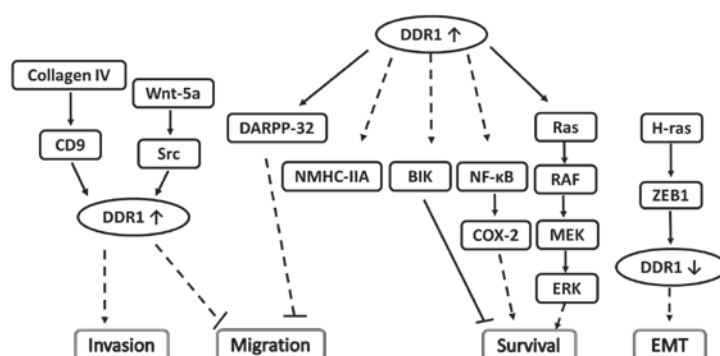


Figure 1. Reported DDR1-associated signaling pathways in breast cancer cells. The mechanisms for the effect of ZEB1, COX-2, DARPP-32 and Wnt-5a on the migration, survival, EMT and invasion regulatory networks are illustrated. Solid lines indicate direct interactions or effects, whereas dashed lines indicate indirect interactions or effects through one or more intermediate steps. Pointed and flat arrows indicate activating and inhibiting effects, respectively. DDR1, discoidin domain receptor 1; ZEB1, zinc finger E-box-binding homeobox 1; COX-2, cyclooxygenase-2; DARPP-32, dopamine- and cAMP-regulated neuronal phosphoprotein; EMT, epithelial-to-mesenchymal transition; CD9, cluster of differentiation 9; NMHC-IIA, non-muscle myosin heavy chain-IIA; BIK, Bcl-interacting killer; NF-κB, nuclear factor-κB; MEK, ERK activator kinase; ERK, extracellular signal-regulated kinase.

breast cancer cells, DDR1 mediates matrix metalloproteinase (MMP)-2 and -9 secretion and invasion induced by native type IV collagen. In NIH3T3 fibroblasts and MCF7 breast cancer cells, DDR1 was demonstrated to inhibit cell spreading, but to promote migration, via interaction with non-muscle myosin heavy chain-IIA, a contractile protein associated with cell spreading (57). Furthermore, native type IV collagen induces a transient increase of CD9-cell surface levels and cell migration through a DDR1 and CD9-dependent pathway in MDA-MB-231 breast cancer cells (58). Therefore, numerous studies demonstrate that DDR1 performs a pro-migratory function (Fig. 1).

However, Hansen *et al* (59) reported an opposite effect of DDR1; they identified that in the MCF-7 and MDA-MB-231 breast cancer cell lines, DDR1 suppressed migration when co-expressed with its interacting partner, dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32). In the presence of DDR1, DARPP-32 was confined to a restricted subcellular location at the plasma membrane, which induced an anti-migratory function in various breast cancer cell lines (59). However, this anti-migration function did not require DDR1 activation, in contrast with the study by Neuhaus *et al* (54). Furthermore, Jonsson *et al* (52) reported that a reduced extent of DDR1 tyrosine phosphorylation in Wnt-5a antisense cells promoted cell scattering, enhanced cell motility and impaired cell-collagen interaction. Wnt-5a may activate DDR1 to inhibit migration in non-malignant human mammary epithelial

cells (52). Wnt gene families encode signaling glycoproteins that are associated with embryogenesis and the regulation of normal and pathological cell processes (60-62). Wnts are implicated in tumor formation; the endogenous expression of Wnt-5a is sufficient to enable the collagen-induced phosphorylation of DDR1 receptors in MCF-7 (63-65). Roarty and Serra (66) demonstrated that the negative interference of transforming growth factor-β signaling not only affected the expression of Wnt-5a, but also the phosphorylation of DDR1, a downstream target of Wnt-5a associated with cell migration. Overall, the effect of DDR1 on migration may depend on interacting factors.

6. DDR1 in breast carcinoma invasion

Regarding the role of DDR1 in invasion, accumulating evidence produced with matrigel invasion assays indicates that DDR1 can promote invasion in a number of types of human cancer cell line, including breast (56), lung (8), prostate (9), pituitary adenoma (67), hepatocellular carcinoma (14) and glioma (68,69). The pro-invasive function of DDR1 may be mediated by the upregulation of the expression of MMPs, particularly MMP-2 and MMP-9. The elevated expression of MMPs contributes to the degradation of extracellular matrix components, facilitating cancer cell invasion (56). Products that can suppress the pro-invasion function of DDR1 have been developed; Santa Cruz

Biotechnology have developed two novel antibodies that can inhibit DDR1-mediated Matrigel invasion (68) and DDR1 activation in human MDA-MB-231 cells (58). Therefore, previous studies predominantly support that DDR1 promotes invasion in breast cancer.

7. Effects of DDR1 on the apoptosis or survival of breast cancer cells

Varying DDR1 expression levels have been identified in a variety of types of human cancer. Assent *et al* (70) identified that in breast cancer, DDR1 performed a role in monitoring the cellular microenvironment and triggering apoptosis via the induction of Bcl-2-interacting killer. To confirm that apoptosis could be induced by DDR1, they used siRNA to reduce the DDR1 expression level in MCF-7 cells and incubated them with collagen gels. They determined that the downregulation of DDR1 inhibited apoptosis by ~60% in breast cancer cells. A further study identified that the catalytic activity of membrane type-1-MMP (MT1-MMP) impaired this DDR1-initiated apoptotic program, although the mechanisms by which MT1-MMP may interfere with DDR1-initiated signaling remain unclear (70).

DDR1 can induce pro- (5,44,69,71,72) and anti- (73-75) proliferative effects depending on the cell type. It was previously demonstrated that in KRAS-driven lung adenocarcinoma, DDR1 and Notch co-inhibition suppressed the activation of critical tumor survival-promoting signaling pathways (76). High DDR1 expression may also exhibit a positive effect in the proliferation and/or survival of breast cancer cells (46,77). Ongusaha *et al* (78) demonstrated that the DDR1 receptor could function as a survival effector in wild-type p53-containing breast cancer cells exposed to genotoxic drugs. Furthermore, Fanale *et al* (79) reported that the DDR1 pathway is likely to be an alternative to the established pro-growth and survival signaling pathways in tumor cells, as activated DDR1 significantly increased tumor cell survival *in vitro*. Therefore, we hypothesize that in breast carcinoma, the DDR1 pathway may be pro-apoptotic or pro-survival, depending on the microenvironment.

8. DDR1 enhances the chemoresistance to genotoxic drugs

Previous studies have demonstrated that DDR1 is a direct transcriptional target of p53. In wild-type p53-containing cells exposed to genotoxic drugs, DDR1 can function as a survival effector (78). During genotoxic stress, the inhibition of DDR1 function led to the markedly increased apoptosis of wild-type p53-containing cells via a caspase-dependent pathway (78). Das (80) reported that DDR1 induced cyclooxygenase-2 (COX-2) expression, resulting in enhanced chemoresistance in MDA-MB-435 and T47D breast cancer cells. Subsequent to using short hairpin RNA against DDR1 to eliminate DDR1-mediated COX-2 induction, they identified that the chemosensitivity of the breast cancer cells was increased. They also demonstrated that DDR1 activated the nuclear factor- κ B (NF- κ B) pathway under genotoxic stress. When they inhibited the activation of the NF- κ B pathway, the level of DDR1-induced COX-2 was reduced, leading to enhanced breast cancer cell chemosensitivity. Therefore,

DDR1-mediated COX-2 induction was NF- κ B-dependent (80). However, the effect of DDR1 on genotoxic drug resistance requires further study.

9. Conclusions

The present review described the complex functions of DDR1 in regulating EMT, migration, invasion, apoptosis, survival and chemoresistance to genotoxic drugs in breast carcinoma, as well as illustrating the identified up/downstream signaling molecules that mediate these effects (Table II, Fig. 1). The effects of DDR1 expression in breast carcinoma may depend on the histological type, grade and hormone receptor status of the tumor (Table I). Considering the critical role of collagen-induced DDR1 in the migration, invasion, apoptosis and chemoresistance of breast carcinoma cells, the associated molecular mechanisms require further investigation.

In summary, regulation via DDR1 may be critical for breast tumor suppression or promotion and therefore, the development of small-molecule drugs targeting DDR1 may be a novel strategy for anticancer therapy according to the histological type, grade and hormone receptor status of the breast tumor. To the present day, studies have identified imatinib, nilotinib and dasatinib as DDR1 inhibitors (81,82).

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