**WRITTEN**

**Withdrawn November 5, 2019**

This article has been withdrawn by the authors. An investigation by Harvard Medical School and Massachusetts General Hospital determined that the DDR1 and actin immunoblots in Fig. 2B (right panels) were reused in Fig. 6A. In addition, the Journal raised questions regarding the merged image for control cells in Fig. 4D.

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**DDR1 Receptor Tyrosine Kinase Promotes Prosurvival Pathway through Notch1 Activation**

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DDR1 (discoidin domain receptor tyrosine kinase 1) kinase is highly expressed in a variety of human cancers and occasionally mutated in lung cancer and leukemia. It is now clear that aberrant signaling through the DDR1 receptor is closely associated with various steps of tumorigenesis, although little is known about the molecular mechanism(s) underlying the role of DDR1 in cancer. Besides the role of DDR1 in tumorigenesis, we previously identified DDR1 kinase as a transcriptional target of tumor suppressor p53. DDR1 is functionally activated as determined by its tyrosine phosphorylation, in response to p53-dependent DNA damage. In this study, we report the characterization of the DDR1 receptor tyrosine kinase 1; ETO, etoposide; KD, knocked down; NICD, Notch intracellular domain; TAP, tandem affinity protein purification.

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**3** The abbreviations used are: DDR1, discoidin domain receptor tyrosine kinase 1; ETO, etoposide; KD, knocked down; NICD, Notch intracellular domain; TAP, tandem affinity protein.
ported that DDR1 activation/autophosphorylation can be also triggered in response to p53 or ionizing radiation as well as its transcriptional induction, suggesting that DDR1 can function independently of collagen ligand following p53 expression (19). In an effort to elucidate the function of DDR1, we performed tandem affinity protein (TAP) purification to identify its interacting partners. Surprisingly, we found that DDR1 binds to the Notch1 receptor and induces activation of downstream Notch signaling. Alterations in Notch signaling have been reported in several human malignancies including T-cell acute lymphoblastic leukemia (T-ALL), which harbor Notch-activating translocations. Recently, Notch has been found to be deregulated in several carcinomas (20, 21). Recent evidence has established Notch1 as a key p53 target gene, which is induced upon p53-dependent UV B exposure in skin cells (22, 23). Although there is increasing evidence that Notch signaling can drive the growth of wide range of tumors, the precise molecular mechanisms underlying alteration of this pathway during carcinogenesis are yet to be identified. Importantly, we demonstrate the existence of a novel intracellular mechanism for Notch1 regulation mediated by DDR1. Our findings strongly suggest that deregulated DDR1 activation would result in persistent autonomous activation of Notch signaling and subsequent induction of a Notch-dependent prosurvival pathway and tumorigenesis/carcinogenesis.

**EXPERIMENTAL PROCEDURES**

**Cell Culture, Cell Lines, and Transfections**—293 HEK, T47D, and HCT116 were cultured in DMEM containing 10% fetal bovine serum (FBS) (Invitrogen), 100 mg/ml streptomycin, and 100 units/ml penicillin. C-terminal FLAG- and HA-tagged DDR1 were generated and cultured with 200 µg/ml zeocin and 20 µg/ml puromycin for 5 days. Homogenate of the cells in this study were carried out using tissue lyser (Qiagen) according to the vendor’s instructions.

**DDR1 Complex Purification**—A detailed TAP procedure has been described previously (24). Briefly, U2OS cells stably expressing C-terminal FLAG- and HA-tagged DDR1 were treated in a lysis buffer (50 mM Tris, pH 7.5, 1% Triton X-100, 0.1% SDS, 150 mM NaCl, 5 mM EDTA, 100 mM NaF, 2 mM Na3VO4, 1 mM DTT, 10% glycerol, 0.5% Nonidet P-40, 5 mM MgCl2) containing protease inhibitors and 0.1% SDS, 150 mM NaCl, 5 mM EDTA, 100 mM NaF, 2 mM Na3VO4, 1 mM DTT, 10% glycerol, 0.5% Nonidet P-40, 5 mM MgCl2) containing protease inhibitors followed by incubation for 1 h on ice. The proteins from nuclear (HRP)-conjugated secondary antibodies were incubated in 5% milk-PBST for 1 h at room temperature. Bands were visualized by Western Lightning Plus-ECL (PerkinElmer Life Sciences).

**Immunoprecipitation (IP)**—500 µg of total cell extracts for IP were prepared with the cell lysis buffer used for Western blotting. Each sample was incubated with 2 µg of antibody and 20 µl of protein A/G-conjugated beads (Santa Cruz Biotechnology) overnight at 4 °C. After three times of spin-down and washing with PBST, the protein-beads complex was subjected to Western blotting.

**Antibodies**—Several commercially available antibodies and other reagents were used in this study. They were the following: anti-FLAG M2 (Sigma), anti-HA (Covance), anti-GST (GE Healthcare), anti-V5 (Invitrogen), anti-DDR1 (Santa Cruz Biotechnology), anti-Notch1 (Santa Cruz Biotechnology), anti-NOTCH1 (Cell Signaling, Val-1744), Hes1 (kindly provided by Dr. G. Paolo Dotto), p53 (BD Biosciences), ERCC1 (Santa Cruz Biotechnology), β-actin (Sigma), bovine or rat tail collagen I (BD Biosciences), and γ-secretase inhibitor (Calbiochem). A specific antibody that recognizes a phosphorylated serine-13 site of human DDR1b was developed in our laboratory (25).

**GST Pulldown**—pGEX 6p-1 was used as vectors expressing GST, GST-Notch1 A (Ankyrin domain of Notch1), and GST-Notch1 B (transcription activation domain of Notch1). Each vector-transformed BL21(DE3) pLysS was induced by 0.5 mM isopropyl 1-thio-β-D-galactopyranoside for 2 h. After sonication, expressed recombinant GST proteins were purified with glutathione-Sepharose 4B (GE Healthcare). 500 µg of total supernatant was added into the GST protein-beads complex and incubated for 2 h at 4 °C. After washing three times with the lysis buffer, the precipitated samples were subjected to SDS-PAGE.

**Western Blotting**—Cells were treated in a lysis buffer as above. Proteins were quantified with the Bio-Rad Protein Assay kit. Equal amounts of protein per sample were subjected to SDS-PAGE and transferred to nitrocellulose membranes (Invitrogen). The membrane was blocked with PBST (PBS containing 0.1% Tween 20) containing 5% skim milk for 1 h. Primary antibodies were incubated in 5% BSA-PBST for 2 h at room temperature or overnight at 4 °C. Horseradish peroxidase-
fraction were prepared from a supernatant by centrifugation at 17,000 × g for 10 min at 4 °C.

**ChIP Assays**—Overall ChIP assays were performed according to the manufacturer’s instructions, using the Chromatin Immunoprecipitation Assay kit (Upstate Biotechnology). Antibody against activated Notch1 (Cell Signaling, Val-1744) was used for ChIP. Binding of active Notch1 to the Hes1 promoter was quantified by real-time PCR in HCT116 cells with or without DDR1 knockdown using the following primers: sense, 5’-CAGACCTTGCTGTGGCG-3’ and antisense 5’-TGTG- ATCCCTAGGCCCTG-3’, with product length of 173 bp corresponding to the -167 to +6 site of the Hes1 promoter.

**Immunofluorescence**—Cells grown on coverslips were fixed with 3.7% (v/v) formaldehyde for 20 min and washed three times with PBST followed by permeabilization with 0.2% Triton X-100 for 5 min. PBST containing 3% BSA was used for blocking. Primary antibody was added and incubated for 3 h. After washing three times with PBST and air drying, the coverslips were mounted with Gel Mount (Biomed, CA).

**TUNEL Assay**—TUNEL assays were performed with the TUNEL assay kit (In Situ Cell Death Detection kit TMR Red; Roche Applied Science). HCT116 cells that were treated with DDR1 activation domain (Notch1A in Fig. 1D), were identified by mass spectrometry as binding partners of DDR1. Among these potential DDR1-interacting proteins, the intracellular part of the Notch1 receptor is of great interest. Accumulating evidence strongly indicates that Notch signaling participates in neoplastic transformation and survival of tumor cells (27). One of the key roles of Notch in promoting tumor progression is to facilitate tumor cell escape from apoptosis (28). Recently, Notch1 was shown to be a p53 target and to function as a protective antiapoptotic mechanism in keratinocytes whereas Notch1 has been shown to have a pro- or anti-apoptotic function depending on the context and/or cell type (22).

First, we confirmed the presence of cleaved Notch1 in DDR1 purification by Western blotting (Fig. 1A, right). The interaction between Notch1 and DDR1 was further validated by reciprocal IP (Co-IP) from 293T cells which were transiently transfected with V5-Notch1 and FLAG-DDR1 (Fig. 1B). To test whether endogenous DDR1 also interacts with Notch1, we performed Co-IP using DDR1 and Notch antibodies on 293T cells with stably transfected Notch1. We were able to confirm the interaction (Fig. 1C). These data confirmed their endogenous interactions (Fig. 1D). To identify the Notch1 receptor as a DDR1-binding partner, in vitro GST pull-down of the Notch1 ankyrin domain (Notch1A in Fig. 1D), was incubated with GST, GST-DDR1, or GST-Ankyrin domain (Notch1B in Fig. 1D). We also confirmed their endogenous interactions (Fig. 1D). The interaction between DDR1 and Notch1B (transcription activation domain) (Fig. 1D).

**RESULTS**

**Identification of Notch1 Receptor as a DDR1-binding Partner via TAP Purification**—We proposed to elucidate the function of DDR1 by studying interacting partners. To understand the protein network involved in DDR1 receptor-mediated cell survival pathway, we used the TAP purification approach (24) to identify cellular factors that interacted with DDR1. We expressed FLAG-HA-double-tagged human full-length DDR1 in U2OS cells. Cell extracts were subjected to sequential purification with anti-FLAG and anti-HA antibody resins. Silver staining of a representative purification is shown in Fig. 1A. Several polypeptides, including RAD50, CDC-54, Notch1, N-GTP-binding protein 2, AC-A synthetase, SRP54, UL61, and K-3-kinase, were identified by mass spectrometry as binding partners of DDR1. Among these potential DDR1-interacting proteins, the intracellular part of the Notch1 receptor is of great interest. Accumulating evidence strongly indicates that Notch signaling participates in neoplastic transformation and survival of tumor cells (27). One of the key roles of Notch in promoting tumor progression is to facilitate tumor cell escape from apoptosis (28). Recently, Notch1 was shown to be a p53 target and to function as a protective antiapoptotic mechanism in keratinocytes whereas Notch1 has been shown to have a pro- or anti-apoptotic function depending on the context and/or cell type (22).

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ment, whereas DDR1 knockdown cells showed no obvious induction of mRNA levels of both Notch1 targets (Fig. 2C).

**DDR1 Activation Enhances Notch1 Activity**—The best characterized canonical pathway of Notch activation involves two proteolytic cleavages mediated by ligand binding. The first is catalyzed by an extracellular ADAM metallloprotease and is followed by the second cleavage event mediated by γ-secretase, which releases the activated NICD. NICD then translocates to the nucleus, where it associates with the DNA-binding protein RBP-jk, converting it from a repressor into an activator of transcription. Thus, we evaluated the functional consequences of DDR1 activation on Notch1 signaling by analyzing the effect on the DDR1-mediated nuclear translocation of Notch1 and on the transcription of Notch1 target genes. To assess whether
inhibition of DDR1 suppresses Notch1 translocation to the nucleus, we extracted nuclear fractions from control or DDR1 knocked down (KD) cells and performed Western blotting analysis. Collagen I-mediated DDR1 activation significantly increased NICD in the nuclear fraction on control (luciferase shRNA) KD cells (Fig. 3A). However, DDR1 KD cells did not show an increase of active form of Notch1 in the nuclear fraction (Fig. 3A). To confirm the DDR1-mediated Notch1 translocation in the nucleus, we transiently transfect a V5-tagged full-length Notch1 expression construct (pcDNA4-Notch1-V5) (29) into DDR1-depleted or control (luciferase shRNA) HCT116 cells. As shown in Fig. 3B, DDR1 KD cells failed to show nuclear localization of Notch1-V5 upon collagen treatment whereas nuclear stained Notch1-V5 appeared in collagen I-treated control KD HCT116 cells. The failure of cells lacking DDR1 to induce HES1 expression upon collagen treatment strongly suggests that DDR1 is required for Notch1-mediated control of target genes transcription. Thus, we investigated the binding of the activated portion of the Notch1 molecule to the Hes1 promoter in HCT116 cells with or without DDR1 knockdown. As shown in Fig. 3C, DDR1 depletion by shRNA approach inhibited the binding of endogenous activated Notch1 to the RBP-jK binding site of the
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FIGURE 3. Notch1 is activated through DDR1 by collagen I. A, c-Notch1 activated by collagen I was translocated to the nucleus. HCT116 cells transfected with control-shRNA and DDR1-shRNA, respectively, were treated with collagen I for the indicated times. Each sample was followed by cell fractionation by the method mentioned under "Experimental Procedures." Nuclear fractions from each sample were subjected to Western blotting to visualize cleaved-Notch1 for activated Notch1 and ERCC1 as a loading control for nuclear fraction. B, fluorescent microscope shows localization to the nucleus of activated Notch1 by collagen I. HCT116 cells stably expressing control and DDR1-shRNA were transfected with V5-tagged Notch1 for 48 h and then treated with collagen I for 2 h. DAPI for nucleus and anti-V5 antibody for transected Notch1 were used. C, binding of active Notch1 to the HES1 promoter was quantified by ChIP assay and real-time PCR in HCT116 cells with or without DDR1 knockdown.

HES1 promoter as assessed by chromatin immunoprecipitation (ChIP) using a primer pair to amplify the RBP-jK binding site of the human HES1 promoter.

DDR1-mediated Intracellular Activation of Notch1—To elucidate further the role of DDR1 signaling in the Notch1 pathway, we examined the direct effect of DDR1 activation on Notch1 activation in the absence of the extracellular domain of Notch1 that is required for the binding of ligands such as Delta and Jagged families. We proposed the hypothesis that there is the existence of a novel intracellular mechanism for Notch1 regulation mediated by DDR1. To investigate this, we stably transfected T47D cells with an extracellular domain-deleted Notch1 mutant (ΔE-Notch1: FLAG-Notch1ΔE-HA in pcDNA3.1; Fig. 4A) or vector alone (pcDNA3.1). Upon collagen treatment, ΔE-Notch1-transfected T47D cells gradually increased the levels of cleaved/active form of Notch1 (c-Notch1) after 2 h whereas vector-transfected T47D cells did not show any increase of c-Notch1 expression (Fig. 4B). In addition, quantitative RT-PCR analysis showed that expression of the endogenous Notch1 target gene Hes1 is induced by collagen treatment in T47D cells expressing ΔE-Notch1 but not in DDR1 knockdown T47D cells (Fig. 4C). We further assessed whether nuclear localization of active ΔE-Notch1 was present upon collagen treatment. Upon collagen I treatment, T47D cells expressing ΔE-Notch1 appeared to contain nuclear staining of c-Notch1 (Fig. 4D) whereas the depletion of DDR1 expression resulted in no specific nuclear staining of active form of Notch1 (data not shown). Together, these data suggest that DDR1 activation leads to intracellular Notch1 activation.

Notch1 Is Critical for DDR1-mediated Cell Survival—We previously proposed that DDR1 activation or overexpression results in increased cell survival, and chemosensitivity to genotoxic stress. Here, we present here the role of DDR1-mediated apoptosis, and chemosensitivity to genotoxic drugs in cancer cells (30). Moreover, we present here evidence that DDR1 regulates DDR1-mediated prosurvival effect on genotoxic stress-induced cell death/apoptosis. To investigate the effects of DDR1 inhibition on cell death, we used a specific inhibitor, DAPT. HCT116 cells were exposed to a genotoxic agent, etoposide (ETO, 40 μM), with or without DDR1 activation by collagen I treatment. Cells exposed to ETO were also treated with or without DAPT. As shown in Fig. 5, DDR1 activation by collagen I treatment inhibited ETO-induced cell death, and addition of DAPT significantly rescued ETO-induced cell death in HCT116 cells. The results suggest that DDR1 exerts prosurvival effect, at least in part, through Notch1 signaling. In this study, we provide evidence that the DDR1 receptor can function as a survival effector through Notch1 signaling, and we strongly suggest the existence of a novel intracellular mechanism for Notch1 regulation mediated by DDR1.

DDR1 Knockdown Reduces Tumorigenicity of HCT116 Cells in Vitro and in Vivo—we also examined the effect of DDR1 knockdown on tumorigenicity, using in vitro colony formation assay/colony forming assay and anchorage-independent growth in soft agarose, as well as in vivo xenograft studies. We used two different shRNA sequences to knock down DDR1 expression (sequences 1 and 2) (Fig. 6A). As shown in Fig. 6B, DDR1 knockdowns significantly suppressed colony numbers and size of colonies compared with control cells. Next, we tested whether DDR1 knockdown affects tumor progression in vivo, using HCT116 nude mouse xenograft model. In an ectopic (subcutaneous) injection experiment, nude mice were injected with HCT116 cells expressing either control shRNA (luciferase) or two different DDR1 shRNAs (1 and 2). Seven mice were injected with each cell population (2 × 10⁶ cells). As shown in Fig. 6C, HCT116 cells expressing DDR1-shRNAs showed a...
highly decreased overall tumor size (~1.5 cm³) compared with that shown by HCT116 cells expressing a control luciferase shRNA (~5 cm³). Tumor weights were also consistent with the sizes. Tumors harvested after 4 weeks of growth were processed for the measurement.

We report here that DDR1 receptor kinase up-regulation/activation induces Notch1 signaling to promote cell survival in cancer cells and that inhibition of DDR1 function enhances cell killing effects in response to genotoxic stress/DNA damage, thus DDR1 activation represents an essential mechanism affecting Notch1-mediated cellular effects. It is well established that the wide range of genetic, environmental, and metabolic stimuli that activate p53 clearly distinguishes it from other known tumor suppressor genes (31). We have previously shown that DDR1 is a direct p53 target gene and can be functionally activated/phosphorylated in a p53-dependent manner (19). We also found that inhibition of DDR1 function resulted in increased apoptosis of wt-p53-containing cancer cells in response to genotoxic stress (30), suggesting that, unlike other p53 target genes that function as either cell cycle inhibitors or apoptosis promoters, DDR1 kinase acts to promote cell survival by counteracting p53-mediated cell death/apoptosis. Thus, DDR1 may be part of a cellular regulatory switch that dictates the cellular decision to undergo either survival or apoptosis in response to genotoxic stress. Accumulating evidence suggests that an aberrant signaling through DDR1 kinase is closely associated with various steps of tumorigenesis and carcinogenesis (10, 15), although little is known about the molecular mechanism(s) underlying the role of DDR1 in cancer. Recently, DDR1 was found as one of several major activated tyrosine kinases and
also was found in somatic mutations in non-small cell lung tumors as well as in acute myeloid leukemia (16, 17, 32). Upregulation of DDR1 is a feature of highly invasive tumor cells including breast cancer cells, suggesting an involvement of DDR1 in tumor progression (33).

Our present studies show that DDR1 acts as a novel upstream regulator for Notch1 signaling, that Notch1 functions as an important effector for DDR1-mediated survival in both the p53-dependent and p53-independent responses to genotoxic stress. It has been reported that Notch signaling can exert either
a pro- or antiapoptotic function in a manner that is highly cell- and context-dependent (23, 34). In neuronal progenitor cells, Notch activation leads to apoptosis through increased nuclear accumulation of p53 and subsequent up-regulation of its pro-apoptotic targets (35). Similarly, in B cell leukemia cells, activation of Notch signaling and induction of its downstream target HES1 lead to growth arrest and cell death (36). A variety of mechanisms have been implicated in the Notch prosurvival function, which include the induction of p21 expression in myeloma cells, and, in cervical cancer cell lines, the induction of PI3K/AKT/mTOR signaling through the noncanonical Notch pathway (37, 38). Other potential cell survival mechanisms in myeloma cells, and, in cervical cancer cell lines, the induction of apoptotic targets (35). Similarly, in B cell leukemia cells, activation of Notch signaling and induction of its downstream targets (35).

Importantly, despite the mounting evidence that deregulated expression and/or activity of wild-type Notch receptor occurs frequently in human malignancies and that constitutively active Notch receptors have transforming activity, thus far the molecular mechanism of wild-type Notch activation in tumorigenesis has been controversial. Extracellular deletions of Notch1 resulting in constitutive activation of the receptor have been implicated in T cell acute lymphoblastic leukemia. Similar truncated receptors have transforming activity in vitro and in animal models (43). However, truncated receptors are uncommon in human malignancies, and no genetic lesions of the Notch locus have been described in human tumors. Therefore it has been suggested that subversion of Notch signaling might play a role in other routes of Notch signaling (ligands) or inside (autocrine) carcinogenesis. Indeed, truncated Notch1 has been described in certain human tumors. In contrast, the molecular mechanism of autocrine activation of wild-type Notch receptors in spontaneous tumor progression, survival, and resistance have yet to be discovered. Our data indicate that activation of DDR1 mediates generation of the intracellular form of Notch1 in the absence of the extracellular domain, i.e., in a ligand-independent fashion. These findings suggest that DDR1, on binding to the transcription activation domain, produces a conformational change in Notch1 that could favor processing by γ-secretase and generation of NICD. Importantly, our study suggests the existence of a novel intracellular mechanism for Notch1 regulation mediated by DDR1. These findings implicate that deregulated DDR1 activation would result in persistent autonomous activation of Notch signaling in these cells and subsequent induction of Notch-dependent prosurvival pathway and/or tumorigenesis/carcinogenesis. Understanding the molecular mechanism underlying p53/DDR1-dependent activation of Notch receptors in vitro and in vivo is expected to eventually translate into novel therapeutic approaches to target Notch in a broad range of diseases.

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WITHDRAWN

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