Protein Kinase C δ Regulates Function of the DF3/MUC1 Carcinoma Antigen in β-Catenin Signaling*

Received for publication, January 15, 2002, and in revised form, February 28, 2002
Published, JBC Papers in Press, March 4, 2002, DOI 10.1074/jbc.M200436200

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The DF3/MUC1 mucin-like glycoprotein is aberrantly overexpressed in most human carcinomas. The MUC1 cytoplasmic domain interacts directly with β-catenin, a component of the adherens junction of mammalian epithelial cells. The present results demonstrate that MUC1 associates with protein kinase Cδ (PKCδ). A TDR sequence adjacent to the β-catenin binding motif in the MUC1 cytoplasmic domain functions as a site for PKCδ phosphorylation. We show that phosphorylation of MUC1 by PKCδ increases binding of MUC1 and β-catenin in vitro and in vivo. The functional significance of the MUC1-PKCδ interaction is further supported by the demonstration that mutation of the PKCδ phosphorylation site abrogates MUC1-mediated decreases in binding of β-catenin to E-cadherin. We also show that the stimulatory effects of MUC1 on anchorage-independent growth are abrogated by mutation of the PKCδ phosphorylation site. These findings support a novel role for PKCδ in regulating the interaction between MUC1 and the β-catenin signaling pathway.

The protein kinase C (PKC) family of serine/threonine protein kinases is involved in intracellular signaling pathways that regulate growth, differentiation, and apoptosis. The PKC isoforms have been divided into: (i) the conventional PKCs (cPKCs; α, β, γ) which are dependent on calcium and activated by diacylglycerol or 12-O-tetradecanoylphorbol-13-acetate (TPA); (ii) the novel PKCs (nPKCs; δ, ε, η) which are calcium-independent and activated by diacylglycerol or 12-O-tetradecanoylphorbol-13-acetate; and (iii) the atypical PKCs (aPKCs; ζ, η) which are calcium-independent and not activated by diacylglycerol or 12-O-tetradecanoylphorbol-13-acetate (1, 2). Of the 12 known PKC isoforms, the ubiquitously expressed PKCδ is unique as a substrate for tyrosine phosphorylation in response to activation of the epidermal growth factor receptor (EGFR) (3), the platelet-derived growth factor receptor (4), or the insulin-like growth factor I receptor (4). Transformation by Ras (5) or v-Src (6) also results in phosphorylation of PKCδ on tyrosine. Interactions between PKCδ and EGFR or c-Src have supported a role for PKCδ as a tumor suppressor (7, 8). Other studies have provided support for involvement of PKCδ in the apoptotic response of cells to genotoxic and oxidative stress (9–12). Targeting of PKCδ to mitochondria induces apoptosis through loss of the mitochondrial transmembrane potential, release of cytochrome c, and activation of caspase-3 (12–15).

The human DF3/MUC1 mucin-like transmembrane glycoprotein is expressed on the apical borders of normal secretory epithelial cells and at high levels over the entire surface of carcinoma cells (16). The MUC1 protein consists of an N-terminal ectodomain with variable numbers of 20 amino acid tandem repeats that are extensively modified by O-glycosylation (17, 18). The MUC1 ectodomain associates with a ~25-kDa C-terminal proteolytic fragment as a heterodimer at the cell surface. The C-terminal subunit includes a transmembrane domain and a 72-amino acid cytoplasmic domain (CD). β-Catenin, a component of the adherens junction of mammalian epithelial cells, binds directly to the MUC1/CD at a serine-rich motif that is similar to β-catenin-binding sites on E-cadherin and the adenomatous polyposis coli (APC) tumor suppressor (19). MUC1 competes with E-cadherin, but not APC, for binding to β-catenin (20). The interaction between MUC1 and β-catenin is down-regulated by phosphorylation of the MUC1/CD by glycogen synthase kinase 3β (GSK3β) (20). Conversely, phosphorylation of MUC1 by c-Src stimulates binding of MUC1 to β-catenin (21). The recent findings that EGFR-mediated phosphorylation of MUC1 regulates the interaction of MUC1 with c-Src and β-catenin has suggested that aberrant overexpression of MUC1 in human carcinoma cells could contribute to the transformed phenotype by dysregulation of EGFR signaling (22, 23).

The present studies demonstrate that PKCδ interacts with MUC1. A T41DR motif in the MUC1/CD has been identified as a PKCδ phosphorylation site. The results show that PKCδ regulates binding of MUC1 to β-catenin and that the T41A mutant abrogates the effects of MUC1 on anchorage-independent cell growth.

MATERIALS AND METHODS

Cell Culture—Human ZR-75–1 breast carcinoma cells were grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum, 100 units/ml penicillin, 100 μg/ml streptomycin, and 2 mM l-glutamine. Human 293 embryonal kidney (ATCC, Manassas, VA) and HCT116 colon carcinoma (24) cells were cultured in Dulbecco’s modified Eagle’s medium and Dulbecco’s modified Eagle’s medium/F-12, respectively, with 10% heat-inactivated fetal bovine serum and antibiotics.

Cell Transfections—293 and HCT116 cells were transiently transfected with control vectors (pIRESpuro2, pEGFP-C1), pIRESpuro2-MUC1 (K378R) (14) in the presence of LipofectAMINE (Invitrogen). Transfection efficiency as determined by immunofluorescence microscopy for MUC1 expression (23) and fluorescence microscopy for GFP expression, ranged from 70 to 80% for 293 cells and 25–30% for HCT116 cells. To establish stable lines, HCT116 cells transfected with pIRESpuro2, pIRESpuro2-MUC1, or pIRESpuro2-MUC1(T41A) were selected in the presence of 0.4 mg/ml puromycin (Calbiochem-Novabiochem, San Diego, CA).
RESULTS

MUC1 Binds Directly to PKCθ—To determine whether MUC1 associates with PKCθ, lysates from human ZR-75-1 cells were subjected to immunoprecipitation with anti-MUC1 and, as a control, IgG. Immunoblot analysis of the precipitates with anti-PKCθ demonstrated the detection of MUC1/PKCθ complexes (Fig. 1A, left). In the reciprocal experiment, immunoblot analysis of anti-PKCθ immunoprecipitates with anti-MUC1 confirmed that MUC1 associates with PKCθ (Fig. 1A, right). By contrast, there was no detectable interaction between MUC1 and PKCθII, PKCβ or PKCα (Fig. 1B). To extend these findings, 293 cells, which are negative for MUC1 (20), were transfected to express MUC1 or MUC1 + PKCθ. Immunoblot analysis of anti-MUC1 immunoprecipitates with anti-PKCθ demonstrated binding of MUC1 with endogenous PKCθ (Fig. 1C). Moreover, coexpression of MUC1 and PKCθ resulted in increased formation of MUC1-PKCθ complexes (Fig. 1C). To assess whether binding is direct, purified GST or a GST fusion protein containing the MUC1/CD (GST-MUC1/CD) was incubated with recombinant PKCθ. Adsorbates to glutathione beads were subjected to immunoblot analysis with anti-PKCθ. The finding that PKCθ binds to GST-MUC1/CD and not to GST alone supported a direct interaction (Fig. 1D).

PKCθ Phosphorylates MUC1 on T41—To determine whether PKCθ regulates function of the DF3/MUC1 Carcinoma Antigen

Purified His-tagged, wild-type and mutant MUC1/CD proteins were incubated with 0.3 μg of recombinant PKCθ (PanVera Corp., Madison, WI). The adsorbates were analyzed by immunoblotting with anti-PKCθ. His-tagged wild-type MUC1/CD and MUC1/CD(T41A) were incubated with 0.3 μg of recombinant PKCθ (PanVera) for 1 h at 4°C. Anti-PKCθ immunoprecipitates were analyzed by immunoblotting with anti-MUC1/CD (20) and anti-PKCθ. In other experiments, purified His-tagged wild-type and mutant MUC1/CD proteins were incubated with 0.3 μg of PKCθ (PanVera) in the absence and presence of 200 μM ATP for 20 min at 30°C. GST-β-catenin bound to glutathione beads was then added, and the reaction was incubated for 1 h at 4°C. The precipitated proteins were subjected to immunoblot analysis with anti-MUC1/CD (20).

In Vitro Phosphorylation—Purified His-tagged, wild-type and mutant MUC1/CD proteins were incubated with 0.3 μg of recombinant PKCθ (PanVera) in kinase buffer (20 mM Tris-HCl, pH 7.6, 10 mM MgCl2, 5 mM dithiothreit) for 20 min at 30°C. Phosphorylated proteins were separated by SDS-PAGE and analyzed by autoradiography.

Anchorage-independent Growth—Cells (4 × 105) were suspended in 1.5 ml of 0.33% Noble agar (DIFCO, Detroit, MI) in Dulbecco's modified Eagle's medium supplemented with 10% heat-inactivated fetal bovine serum and antibiotics. The cell suspension was layered over 3.5 ml of Iscove's modified Eagle's medium in 60-mm dishes. One ml of fresh culture medium was added at 2 weeks. Colonies composed of >10 cells were counted at 3 weeks.

MUC1/CD is a substrate for PKCθ, we incubated purified His-MUC1/CD with recombinant PKCθ and [γ-32P]ATP. Analysis of the reaction products by SDS-PAGE and autoradiography demonstrated phosphorylation of MUC1/CD (Fig. 2A). A ST41DRS site in MUC1/CD conforms to the preferred (S/T)X(K/R) motif for PKCθ phosphorylation. To determine whether ST41DRS is...
PKCδ Regulates Function of the DF3/MUC1 Carcinoma Antigen

Equal loading of the MUC1/CD proteins was assessed by Coomassie Blue staining (middle panel, left). Equal loading of recombinant PKCδ was confirmed by immunoblot analysis with anti-PKCδ (lower panel, left). Purified MUC1/CD and MUC1/CD(T41A) were incubated with recombinant PKCδ. Anti-PKCδ immunoprecipitates were analyzed by immunoblotting with anti-MUC1/CD (upper panel, right) and anti-PKCδ (lower panel, right). Histidine-MUC1/CD or Histidine-MUC1/CD(T41A) were incubated with PKCδ and ATP. Controls were performed in the absence of PKCδ or ATP. After incubation at 37 °C, GST-β-catenin bound to glutathione beads was added for 1 h at 4 °C. The adsorbates were analyzed by immunoblotting with anti-MUC1/CD and anti-β-catenin.

Fig. 2. PKCδ phosphorylates MUC1 on Thr41. A, GST or GST-MUC1/CD was incubated with PKCδ and [γ-32P]ATP. As a control, GST-MUC1/CD was incubated with [γ-32P]ATP in the absence of PKCδ. The reaction products were analyzed by SDS-PAGE and autoradiography. B, schematic representation of wild-type MUC1/CD and the Ser/Thr Thr → Ala mutants. The specified sequences represent mutations made in the entire cytoplasmic domain. Numbers (1–72) reflect amino acids in the CD. TR, tandem repeats. TM, transmembrane region. CD, cytoplasmic domain. C, purified MUC1/CD and the indicated mutants were incubated with PKCδ and [γ-32P]ATP. The reaction products were analyzed by SDS-PAGE and autoradiography (upper panel, left). Densitometric scanning of the signals obtained with MUC1/CD and the mutants is expressed as fold intensity relative to that for MUC1/CD (WT). Phosphorylation by PKCδ, we mutated this site in MUC1/CD to SA41DRS (Fig. 2B). PKCδ-mediated phosphorylation of MUC1/CD(T41A) was attenuated compared with that obtained with wild-type MUC1/CD (Fig. 2C, left). By contrast, phosphorylation of MUC1 by PKCδ was unaffected by Ser → Ala mutations of either or both of the flanking serines (Fig. 2C, left). The results also demonstrate that autophosphorylation of PKCδ is decreased in the presence of MUC1/CD(T41A) (Fig. 2C, left). To determine whether the T41A mutation affects binding of PKCδ, wild-type MUC1/CD and MUC1/CD(T41A) were incubated with recombinant PKCδ. Immunoblot analysis of anti-PKCδ immunoprecipitates with anti-MUC1/CD demonstrated that PKCδ binds equally to wild-type MUC1/CD and MUC1/CD(T41A) (Fig. 2C, right). Previous studies have shown that phosphorylation of the MUC1/CD Ser44 site by GSK3β decreases the interaction between MUC1/CD and β-catenin (20). To assess the effects of PKCδ-mediated phosphorylation of MUC1/CD, we incubated MUC1/CD with PKCδ in the presence and absence of ATP. After phosphorylation of MUC1/CD, GST or GST-β-catenin was added for 1 h at 4 °C. Proteins precipitated with glutathione beads were analyzed by immunoblotting with anti-MUC1/CD. As shown previously, MUC1/CD binds to GST-β-catenin and not GST (20). Preincubation of MUC1/CD with PKCδ and ATP was associated with a higher level of MUC1/CD binding to GST-β-catenin than that obtained in the absence of PKCδ or ATP (Fig. 2D). By contrast, preincubation of MUC1/CD(T41A) with PKCδ and ATP had no detectable effect on binding of MUC1/CD(T41A) to β-catenin (Fig. 2D). The finding that, in the absence of PKCδ phosphorylation, less β-catenin binds to MUC1/CD(T41A) as compared with that for wild-type MUC1/CD may reflect conformational effects of the T41A mutation on the β-catenin-binding site (Fig. 2D). These findings demonstrate that PKCδ phosphorylates MUC1/CD on Thr41 and thereby increases binding of MUC1/CD and β-catenin.

PKCδ Regulates Interaction of MUC1 with β-Catenin in Vivo—To determine whether PKCδ regulates the interaction between MUC1 and β-catenin in vivo, transfection studies were performed in the MUC1-negative 293 cells. After transfection of vectors expressing MUC1 and PKCδ or the kinase-inactive PKCδ(K-R) mutant, lysates were subjected to immunoprecipitation with anti-MUC1. Immunoblot analysis of the precipitates with anti-β-catenin demonstrated that PKCδ increases the interaction between MUC1 and β-catenin as compared with that in cells transfected with PKCδ(K-R) (Fig. 3A). In concert with these results and involvement of Thr41, PKCδ had little if any effect on binding of β-catenin to the MUC1(T41A) mutant (Fig. 3A). To extend the analysis, we transfected MUC1-negative HCT116 cells to stably express the empty vector, wild-type MUC1, or MUC1(T41A) (Fig. 3B, left). Anti-MUC1 immunoprecipitates from HCT116/V, HCT116/MUC1, and HCT116/MUC1(T41A) cells were subjected to immunoblotting with anti-β-catenin. The results demonstrate that MUC1, but not MUC1(T41A), binds to β-catenin (Fig. 3B, right). When these cells were transfected to express GFP-PKCδ, immunoblot anal-
ysis of anti-MUC1 immunoprecipitates with anti-β-catenin demonstrated that PKCδ induces binding of β-catenin to wild-type MUC1 and not the MUC1(T41A) mutant (Fig. 3B, right). Binding of MUC1 to endogenous PKCδ and ectopically expressed GFP-PKCδ was also decreased with the MUC1(T41A) mutant as compared with that with wild-type MUC1 (Fig. 3B, right). Previous work has demonstrated that MUC1 and E-cadherin compete for binding to β-catenin (20). To determine whether expression of the MUC1(T41A) mutant affects binding of β-catenin to E-cadherin, anti-E-cadherin immunoprecipitates were analyzed by immunoblotting with anti-β-catenin. In concert with previous findings (20), expression of wild-type MUC1 was associated with decreased binding of E-cadherin and β-catenin (Fig. 3C). By contrast, expression of MUC1(T41A) had less of an effect on the interaction of E-cadherin and β-catenin compared with that in HCT116/MUC1 cells (Fig. 3C).

Effects of MUC1 on Anchorage-independent Growth Are Abrogated by the T41A Mutation—To assess the functional significance of the interaction between MUC1 and PKCδ, HCT116/V, HCT116/MUC1, and HCT116/MUC1(T41A) cell lines were analyzed for anchorage-dependent and -independent growth. Expression of wild-type MUC1 or the MUC1(T41A) mutant had no apparent effect on growth in tissue culture compared with that for HCT116/V cells (Fig. 4A). Moreover, while GFP-PKCδ had little additional effect on the interaction of E-cadherin and β-catenin in HCT116/MUC1 cells, expression of both GFP-PKCδ and the MUC1(T41A) mutant resulted in an increase in E-cadherin-β-catenin complexes (Fig. 3C). These findings demonstrate that PKCδ regulates the interaction between MUC1 and β-catenin in cells and thereby binding of E-cadherin with β-catenin.
with HCT116/V cells (Fig. 4B). By contrast, expression of MUC1(T41A) was associated with the formation of colonies that were similar to those found with HCT116/V cells (Fig. 4B). Similar results were obtained with the independently selected clones (Fig. 4B). The number of colonies obtained for HCT116/MUC1 cells was also higher than those found for HCT116/V and HCT116/MUC1(T41A) cells (Fig. 4C). These findings demonstrate that expression of wild-type MUC1 contributes to anchorage-independent growth and that mutation of the PKCδ phosphorylation site abrogates this effect.

**DISCUSSION**

PKCδ has been implicated in the response of cells to activation of the EGFR, platelet-derived growth factor receptor, and insulin-like growth factor I receptors (3, 4). Other findings have supported a role for PKCδ in the apoptotic response of cells to stress (9–15). Functional involvement of PKCδ at the cell membrane has also been shown through regulation of phospholipid scramblase activity during both cell activation and apoptosis (25). The present studies demonstrate that PKCδ interacts with the transmembrane MUC1 protein. The results show that
PKCδ phosphorylates the MUC1 cytoplasmic domain at Thr\textsuperscript{41} (Fig. 4D). Previous work has shown that GSK3β phosphorylates Ser\textsuperscript{44} in the TDRSPYE domain of MUC1/CD (Fig. 4D) (20). In addition, the Tyr\textsuperscript{46} site is phosphorylated by EGFR (23) and c-Src (21) (Fig. 4D). Phosphorylation of Ser\textsuperscript{44} by GSK3β decreases β-catenin binding, while phosphorylation of Tyr\textsuperscript{46} increases the interaction of MUC1 and β-catenin. The present results demonstrate that PKCδ also regulates the formation of MUC1-β-catenin complexes. In vitro binding of PKCδ was similar with wild-type MUC1/CD and the MUC1/CD(T41A) mutant. By contrast, binding of PKCδ to MUC1(T41A) in vivo was decreased compared with that found for wild-type MUC1. These findings suggest that, in the presence of other binding proteins, such as c-Src and GSK3β, the T41A mutation disrupts the interaction between MUC1 and PKCδ. Other work has shown that c-Src disrupts binding of MUC1 and GSK3β (20). Thus, given the proximity of the MUC1 sites for interactions with c-Src, GSK3β, and PKCδ (Fig. 4D), modification of Thr\textsuperscript{41}, Ser\textsuperscript{44}, and/or Tyr\textsuperscript{46} by phosphorylation or mutation may affect the integration of MUC1 signaling with diverse pathways.

The available evidence indicates that MUC1 and E-cadherin compete for binding to the same pool of β-catenin (20). E-cadherin functions in homotypic recognition and the regulation of cell mobility (26). The interaction between E-cadherin and β-catenin is essential for cell adhesion by connecting E-cadherin to α-catenin and thereby the cytoskeleton (27–30). Importantly, disruption of E-cadherin function and cell adhesion has been associated with tumor development (29, 31–33). Other studies have demonstrated that MUC1 affects E-cadherin-mediated cell adhesion (34). The present results demonstrate that PKCδ increases the interaction between MUC1 and β-catenin in vitro and in cells. Moreover, mutation of the MUC1 Thr\textsuperscript{41} phosphorylation site abrogates the effects of PKCδ on formation of MUC1-β-catenin complexes. In the in vitro binding studies indicate that the T41A mutation may also affect the MUC1/CD-β-catenin interaction, perhaps by causing changes in the tertiary structure of the β-catenin-binding site. Nonetheless, while MUC1 decreased binding of E-cadherin and β-catenin in cells, expression of the MUC1(T41A) mutant in part reversed this effect. Whereas enforced expression of PKCδ in HCT116/MUC1(T41A) cells was also associated with increased formation of E-cadherin-β-catenin complexes, these experimental conditions could result in interactions not found with endogenous PKCδ. The findings thus support a signaling pathway in which the interaction between MUC1 and PKCδ increases binding of MUC1 and β-catenin, while decreasing the formation of E-cadherin-β-catenin complexes.

MUC1 is normally expressed at the apical borders of secretory epithelial cells (16). In carcinoma cells, polarization of MUC1 is lost with high levels of expression over the entire cell surface (16, 35). The apical border of the normal glandular epithelium is devoid of cell-cell interactions at the surface lining secretory ducts. Overexpression of MUC1 by carcinoma cells, however, could confer an anti-adhesive function to the entire cell surface by disrupting E-cadherin-mediated homotypic recognition. To address the function of MUC1 on cell growth, MUC1-negative HCT116 cells were stably transfected to express wild-type MUC1 or the MUC1(T41A) mutant. Expression of MUC1 or MUC1(T41A) had no significant effect on adherent growth in tissue culture. By contrast, wild-type MUC1 conferred a substantial increase in anchorage-independent growth in soft agar. These effects could not be attributed to the heavily glycosylated ectodomain because anchorage-independent growth of HCT116 cells expressing similar levels of MUC1(T41A) was comparable with that found with control HCT116/V cells. Rather, the distinct patterns of anchorage-independent growth for HCT116 cells expressing wild-type MUC1 or MUC1(T41A) support direct involvement of the PKCδ phosphorylation site. These findings and the demonstration that PKCδ-mediated phosphorylation of MUC1 regulates binding of MUC1 and β-catenin are in concert with a model in which PKCδ subverts E-cadherin function by titrating binding of β-catenin to MUC1. Conversely, in a simplified model, mutation of MUC1 at Thr\textsuperscript{41} restores binding of β-catenin to E-cadherin and decreases anchorage-independent growth.

In addition to interactions with E-cadherin and MUC1 at the cell membrane, β-catenin binds directly to the APC gene product in the cytosol (36, 37). The interaction between adenoma-polyposis coli and β-catenin regulates β-catenin turnover (38) and alters cell adhesion (39). β-Catenin also forms nuclear complexes with members of the T-cell factor/lymphoid enhancing factor 1 family of transcription factors (40, 41). Loss of APC-mediated regulation of β-catenin in transformed cells is associated with constitutive activation of β-catenin-T-cell factor/lymphoid enhancing factor 1 transcriptional complexes (42–44). The present findings contribute to a role for MUC1 in regulating β-catenin at the cell membrane. While regulation of β-catenin may also occur as a result of binding to MUC1 that accumulates in the cytosol of carcinoma cells (16), there are presently no known functions for MUC1 in control of β-catenin signaling in the nucleus.

Acknowledgment—We appreciate Kamal Chauhan for his excellent technical support.

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J. Biol. Chem. 2002, 277:17616-17622. doi: 10.1074/jbc.M200436200 originally published online March 4, 2002

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