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Critical Review

The Cell Surface Glycoprotein CDCP1 in Cancer—Insights, Opportunities, and Challenges

Andreas Wortmann[1], Yaowu He[1], Elena I. Deryugina[2], James P. Quigley[2] and John D. Hooper[1]
[1]*Institute of Health and Biomedical Innovation and School of Life Sciences, Queensland University of Technology, Kelvin Grove, QLD, Australia*
[2]*Department of Cell Biology, The Scripps Research Institute, La Jolla, CA, USA*

Summary

In the last few years dysregulated expression of the cell surface glycoprotein CUB domain-containing protein 1 (CDCP1) has been associated with several cancers and this cell surface molecule has been recognized both as a tumor marker and as a potential target to disrupt progression of cancer. Here we summarize what is known about CDCP1 including its structural features, expression in normal and cancerous tissues, and the *in vitro* experiments and studies in animal models that have provided the key insights into its potential role in tumor formation and metastasis in humans. We conclude by highlighting opportunities and challenges in targeting CDCP1 in cancer. © 2009 IUBMB

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INTRODUCTION

CUB domain-containing protein 1 (CDCP1) (*1*) is a cell surface glycoprotein also known as *s*ubtractive *im*munization *a*ssociated 135 kDa (SIMA135) (*2*), gp140 (*3*), and *tr*ansmembrane and *a*ssociated with *S*rc *k*inases (Trask) (*4*) and has been assigned the cluster of differentiation (CD) designation CD318. In hindsight, the independent identification of CDCP1, using several different biased genetic and protein based approaches, provided the initial indications of the potential importance of this protein in cancer progression. In the earliest of these reports in 1996, a processed form of CDCP1 was identified as being tyrosine phosphorylated in response to loss of $\alpha_6\beta_4$ integrin-mediated keratinocyte adhesion to laminin (*5*). A few years later, in a study that was the first to provide the complete CDCP1 DNA coding sequence, Scherl-Mostageer et al. used a biased mRNA screening approach to show that the *CDCP1* gene is highly transcribed in lung and colon cancer derived cell lines (*1*). This was followed, in 2003, by the first isolation of the complete CDCP1 protein sequence using a clever *in vivo* immunological approach biased to identify proteins functionally involved in metastasis (*2*). Subsequently, two different groups identified CDCP1 as a Src family kinase (SFK) interacting protein in MDA-468 breast cancer cells (*4*) and A549 lung adenocarcinoma cells (*6*). In two other papers aimed at identifying molecules associated with important signaling proteins, CDCP1 was identified as a protein kinase Cδ (PKCδ) (*7*) and a tetraspanin CD9 (*8*) interacting protein. Strengthening the proposal that CDCP1 has a role in cancer progression, dysregulated CDCP1 expression has been associated with cancer of the lung (*1, 9*), kidney (*10*), colon (*1, 2, 11*), and breast (*1, 12*). In addition, CDCP1 has been suggested as an independent marker for leukemia (*13*). In this review, we summarize CDCP1 structural features and interacting proteins and examine its emerging role, both as a marker for cancer as well as a cancer drug target.

CDCP1 STRUCTURAL FEATURES

CDCP1 is an 836 amino acid cell surface glycoprotein containing a 29-residue amino terminal signal peptide and extracellular, transmembrane, and cytoplasmic domains of 636, 21, and 150 amino acids, respectively (Fig. 1A). The extracellular domain contains three regions with low homology to complement protein subcomponents C1r/C1s, urchin embryonic growth factor, and bone morphogenetic protein 1 (CUB) domains, as well as 14 consensus N-glycosylation sites and 20 cysteines likely involved in disulfide bond formation (*1–4*). Interestingly, 12 of the consensus N-glycosylation sites and 19 of the extracellular cysteines are conserved in human, chimpanzee, dog, cow,

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Address correspondence to: John D. Hooper, Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, QLD 4059, Australia. Tel.: +61-7-31386197. E-mail: jd.hooper@qut.edu.au

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mouse, and rat—N39 is not found in dog, cow, mouse, and rat, N339 is not found in mouse, and C423 is not present in rat (Fig. 1B). The predicted molecular weight of CDCP1, after removal of its signal peptide, is ~90.1 kDa (*2*), whereas by Western blot analysis the apparent molecular weight is 135–140 kDa (*2–4, 7*). Deglycosylation using the enzyme *N*-glycosydase F indicated that between 30 and 40 kDa of the apparent molecular weight is due to the addition of N-linked glycans (*2*). To date, the roles of these extracellular features have not been defined.

CDCP1 INTERACTING PROTEINS

A poorly understood feature of CDCP1 biology is its ability to interact with a growing number of proteins. Perhaps the most interesting of these is the tyrosine phosphorylation-dependent binding of SFKs and PKCδ to CDCP1. Several groups have shown that, consistent with the presence of five conserved intracellular tyrosine residues (Fig. 1), CDCP1 is phosphorylated by SFKs (*2–4, 6, 7*), including Src, Yes, and Fyn (*4, 6, 7*). Significantly, Benes et al. have shown that SFK-mediated phosphorylation of CDCP1 is required for formation of a CDCP1:SFK:PKCδ multiprotein complex. As shown in Fig. 2A, these authors proposed that SFK phosphorylation of CDCP1 is initiated at Y734 resulting in SFK binding at this site, promoting additional phosphorylation at Y743 and Y762, and PKCδ recruitment at CDCP1-p-Y762—the first demonstration of PKCδ as a phosphotyrosine-binding protein (*7*). This observation is significant as it indicates that CDCP1 linkage of SFK tyrosine phosphorylation and PKCδ serine/threonine phosphorylation is likely to be important in normal and disease processes. In fact, Uekita et al. have reported that SFK phosphorylation of CDCP1 confers resistance of lung adenocarcinoma cells *in vitro* to a type of apoptosis, anoikis, initiated by loss of cell contact with the extracellular matrix (*6*). Importantly, it was also shown that CDCP1-mediated tyrosine phosphorylation of PKCδ is required for the observed resistance to anoikis (*6*). Of further relevance to cancer progression, this group has more recently reported that phosphorylation of CDCP1 at Y734 is increased in tumor nodules of gastric cancer 44As3 cells during peritoneal invasion in mice. Moreover, this work also demonstrated elevated CDCP1-p-Y734 levels in human gastric cancers in tumor cells invading the gastric wall (*14*). Consistently, in lung cancer patient samples CDCP1-p-Y734 has been shown to be largely present in invading tumor cells (*9*).

There are also data indicating that 135–140-kDa CDCP1 (referred to here as high molecular weight; HMW-CDCP1) is processed, through interactions with proteolytic enzymes, to a low molecular weight (LMW) form (Fig. 2B). For example, trypsin treatment of keratinocytes *in vitro* generates ~80-kDa CDCP1 via cleavage at, or amino terminal of, E278 (*3, 5*). It appears that similarly sized LMW-CDCP1 species can also be generated by endogenous mechanisms, as treatment of adherent keratinocytes with the polysulfonated membrane impermeable naphthylurea, suramin and several of its analogues, results in the appearance of SFK-phosphorylated LMW- and HMW-CDCP1 (*3*). In addition, similar sized endogenous processed CDCP1 species have been observed in breast cancer MDA-MB-468 cells [referred to as p85; (*4*)] and in several lung (*6*) and gastric (*14*) cancer cell lines (referred to as 70-kDa CDCP1). Although the cellular mechanisms regulating generation of LMW-CDCP1 have not been defined, a number of reports support the involvement of an endogenous tryptic serine protease. Recent supporting data have come from experiments using the trypsin-fold-specific inhibitor ecotin and MDA-MB-468 cells stably transfected with a CDCP1 expression construct. These cells express both LMW and HMW species from the CDCP1 expression construct, indicating that LMW-CDCP1 is not generated by alternate mRNA splicing. Furthermore, ecotin treatment of these cells resulted in a marked reduction in the level of the LMW form, suggestive of serine protease-mediated CDCP1 processing (*4*). Further support has come from experiments showing that plasmin, at subphysiological concentrations, converts HMW-CDCP1-p-Y734 to an ~80-kDa species *in vitro* and homogenates of suramin-treated epidermis from neonatal laminin 5 deficient (*LAMA3−/−*) mice contain both LMW and HMW CDCP1-p-Y734 (*3*). Also, the catalytic domain of the serine protease MT-SP1 (also known as matriptase and TADG-15) cleaves the recombinant extracellular domain of CDCP1 at R368 [Fig. 1A; inadvertently referred to as R369 in (*4*)]. The *in vivo* relevance of MT-SP1-mediated processing of CDCP1 is supported by two observations of cellular interactions involving these proteins. First, Bhatt et al. demonstrated that an anti-MT-SP1 antibody immunoprecipitates myc-tagged CDCP1 from overexpressing MDA-MB-468 cells (*4*), and, second, endogenous MT-SP1 and CDCP1 have been coimmunoprecipitated from SW480 colon cancer cells using an antibody against the tetraspanin CD9 (*8*).

The picture emerging from these reports is that changes in phosphorylation of both LMW- and HMW-CDCP1 are mediated by a number of cellular events including proteolysis and cell adhesion/deadhesion. For example, trypsin treatment of keratinocytes results in loss of HMW-CDCP1-p-Y734 and appearance of LMW-CDCP1-p-Y734. On balance it appears, as proposed by Brown et al. (*3*), that proteolytic conversion results in increased phosphorylation of LMW-CDCP1 as shown in Fig. 2C. However, it is likely that another major contributor to the observed increased in phosphorylation of LMW-CDCP1 is the concurrent loss of cellular contact with matrix components during cell deadhesion. For example, in a key experiment, Xia et al. showed that interruption of keratinocyte integrin $\alpha_6\beta_4$ binding to laminin 5, using an inhibitory anti-laminin 5 monoclonal antibody, increased phosphorylation of LMW-CDCP1 (Fig. 2D, forward arrow). The contribution of cell deadhesion to increased phosphorylation of CDCP1 is also indicated by experiments in which phosphorylated LMW- and HMW-CDCP1 were affinity purified more efficiently from A549 cells grown in suspension than adhesion using a Fyn SH2 domain as bait (*6*).

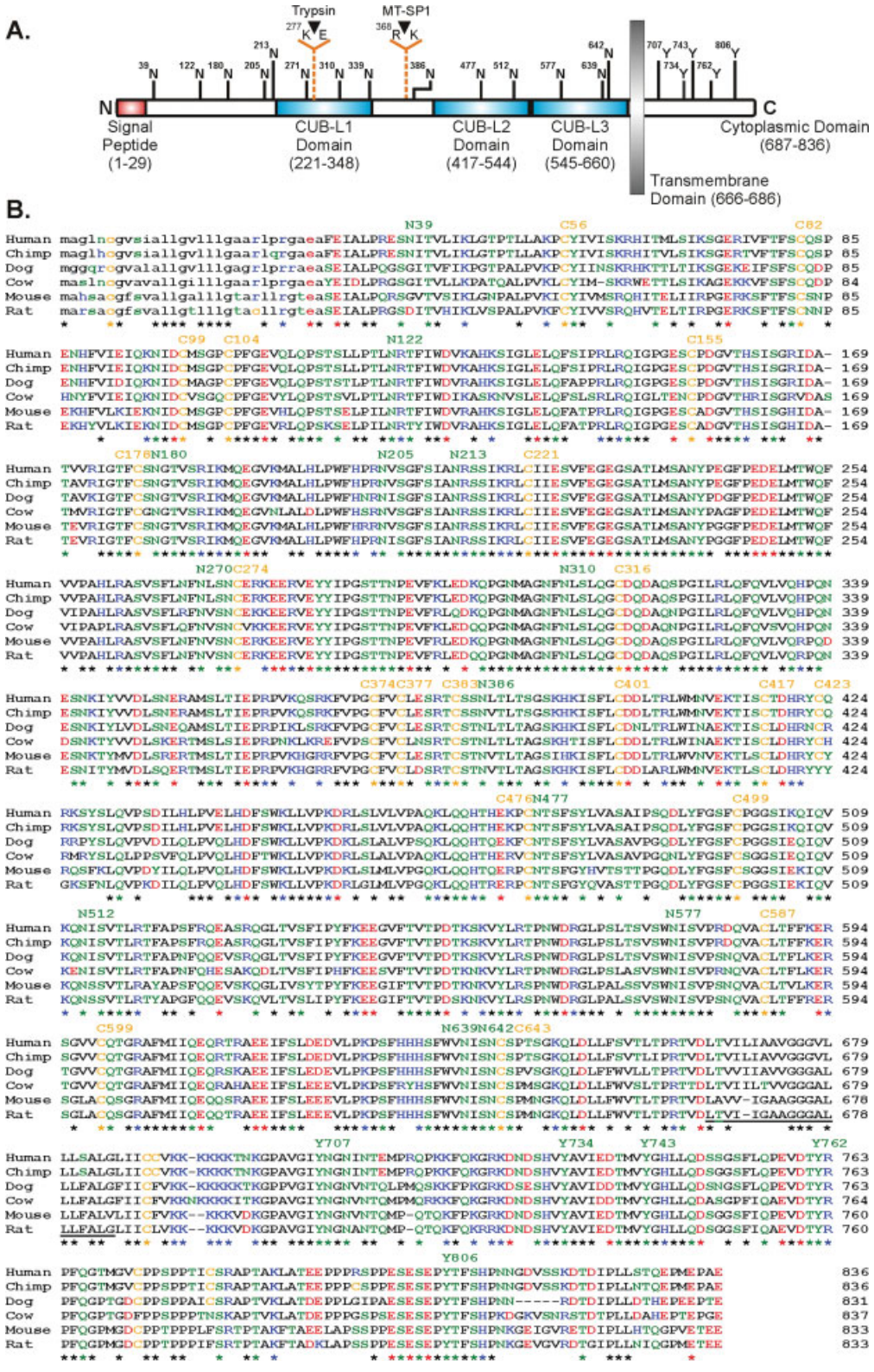

Figure 1. CDCP1. (A) Schematic representation of human CDCP1 structural features including signal peptide, CUB-like domains (CUB-L1 to CUB-L3), transmembrane domain, consensus N-glycosylation sites, and intracellular tyrosine residues. Trypsin and MT-SP1 cleavage sites are indicated. (B) Alignment of the long CDCP1 protein isoform from human (AAO33397), chimpanzee (XP_001147144), dog (XP_541913), cow (XP_612363), mouse (NP_598735), and rat (NP_001100339). Sequence of the signal peptide is in lower case lettering and mature CDCP1 in upper case. Conserved residues are indicated by an asterisk. Asparagines of consensus N-glycosylation sites and extracellular cysteines are numbered above the amino acid sequence. The transmembrane domain is underlined.

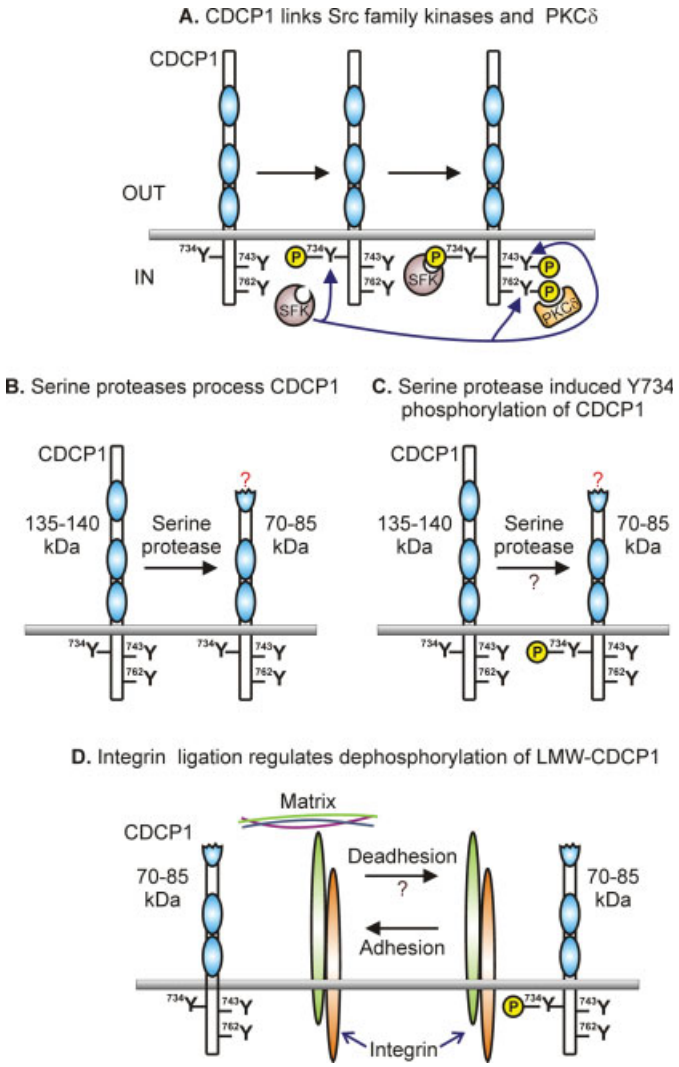

Figure 2. CDCP1 protein interactions. (A) CDCP1 links Src family kinases (SFKs) and PKCδ. SFKs phosphorylate CDCP1-Y734, initiating SFK binding at this site, which in turn promotes additional phosphorylation at Y743 and Y762 and PKCδ recruitment at CDCP1-p-Y762. (B) Serine proteases such as exogenous trypsin, plasmin, and MT-SP1 process CDCP1 from high (135–140 kDa) to low (70–85 kDa) molecular weight species. The question mark (red color) indicates putative site(s) where trypsin, plasmin, and the endogenous processing enzyme cleave high-molecular-weight CDCP1. (C) Serine protease-induced phosphorylation of CDCP1-Y734. It appears that in addition to cleaving CDCP1, trypsin and plasmin also induce phosphorylation of CDCP1-Y734. The black question mark indicates that the relative contributions of proteolysis and cell deadhesion to CDCP1 phosphorylation are not known. (D) Cell deadhesion/adhesion involving changes in integrin ligation with matrix proteins regulates the phosphorylation state of LMW-CDCP1. Adhesion onto laminin 5 via integrins $\alpha_6\beta_4$ and $\alpha_3\beta_1$ results in dephosphorylation of LMW-CDCP1. Loss of adhesion to laminin 5 contributes to phosphorylation of LMW-CDCP1.

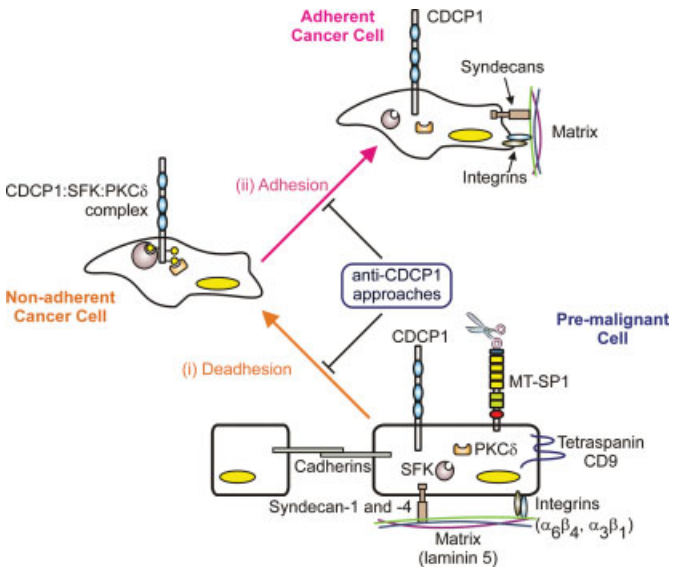

Figure 3. Speculative overview of CDCP1 in premalignant and cancer cells. Shown are CDCP1 interacting proteins including Src family kinases (SFKs), PKCδ, the serine protease MT-SP1 (also known as matriptase and TADG-15), cadherin cell/cell adhesion proteins, syndecan cell/matrix adhesion proteins, and the tetraspanin CD9. CDCP1 is presented on the cell surface as 135–140-kDa and 70–85-kDa species; for simplicity only full-length CDCP1 is shown. Cell deadhesion (i) contributes to tyrosine phosphorylation of CDCP1. The accompanying formation of the CDCP1:SFK:PKCδ complex is mechanistically involved in protecting cells from anoikis (*6, 14*). Cell adhesion (ii) involving integrin ligation to the matrix protein laminin 5 induces dephosphorylation of CDCP1. As cell adhesion and deadhesion are important during various stages of cancer, it is possible that strategies targeting CDCP1 that modulate cell adhesion or deadhesion may represent rational approaches to disrupt cancer progression.

Although the relative contributions of cell deadhesion and proteolysis to CDCP1 phosphorylation remain to be more exactly defined, it is clear that cell adhesion causes dephosphorylation of CDCP1. This has been shown in experiments examining integrin-mediated readhesion of trypsin-suspended keratinocytes to the basement membrane protein laminin 5. These experiments showed that readhesion onto laminin 5 via integrins $\alpha_6\beta_4$ and $\alpha_3\beta_1$ results in dephosphorylation of LMW-CDCP1 (*5*) (Fig. 2D, reverse pathway). A later report from this group showed that readhesion results in the time-dependent dephosphorylation of LMW-CDCP1 and re-expression of HMW-CDCP1-p-Y734 (*3*). Interestingly, this work also demonstrated that dephosphorylation of Y734 in LMW- and HMW-CDCP1 in keratinocytes occurs with different kinetics; whereas suramin-induced phosphorylation of HMW-CDCP1 disappears within 15 min, phosphorylated LMW-CDCP1 lasted for longer than 4 h.

Further complexity in the regulation of CDCP1 is suggested by observations that CDCP1 from overexpressing MDA-MB-468-CDCP1 cells interacts with endogenous cell/cell adhesion proteins N- and P-cadherin and the cell/matrix adhesion proteins syndecan-1 and -4 (*4*). Interestingly, CDCP1 also contains a consensus palmitoylation motif adjacent to its transmembrane domain (*2*) and it is possible that addition of palmitate will regulate plasma membrane localization of LMW- and HMW-CDCP1 as well as interactions with other proteins.

DYSREGULATED EXPRESSION OF CDCP1 IN SOLID TUMORS

Dysregulated CDCP1 expression has been associated with a number of cancers and recent reports suggest a functional role in tumor cells that could potentially be targeted to disrupt cancer progression. In the largest reported examinations of CDCP1 in cancer, studies by Awakura et al. (*10*) and Ikeda et al. (*9*) analyzed the expression of this protein in 230 renal cell carcinoma (RCC) and 200 lung adenocarcinoma patient samples, respectively. In RCC samples, CDCP1 was not detected in normal kidney cells but was expressed in 77 of the 230 cancer cases (33.5%), with expression significantly associated with indicators of advancing disease (tumor stage, histological grade, and presence of metastases). In addition, CDCP1 expression and metastasis were significant predictors of shorter disease-specific survival and, in patients with localized cancer, CDCP1 positive staining and tumor stage >2 were significant predictors of shorter recurrence-free survival (*10*). The analysis of lung adenocarcinoma samples also demonstrated important associations with disease progression (*9*). Sixty of the 200 cases were classified as expressing moderate to high levels of CDCP1. High CDCP1 expression correlated with increased occurrence of lymph node metastasis and tumor relapse with 5-year disease-free and overall survival rates significantly lower for patients with high CDCP1 expression (*9*).

Several other studies have examined CDCP1 mRNA or protein expression in small numbers of cancer samples. For example, as part of the initial report on the CDCP1 gene and coding sequence, elevated CDCP1 mRNA levels were detected in several solid tumors including colon, lung, and breast cancers relative to unmatched normal tissues (*1*). Further support for increased CDCP1 expression in breast cancer came from a study which, although providing no comparison with normal breast tissue, showed that CDCP1 mRNA levels inversely correlated with methylation of the CDCP1 transcription initiation site in all 25 breast cancer patient samples examined (*12*). Consistently, immunohistochemical analysis of two breast cancer samples demonstrated that a patient with high CDCP1 mRNA levels had correspondingly high CDCP1 protein levels that correlated with high expression of the proliferation marker Ki67, while a patient with low CDCP1 mRNA levels had correspondingly low CDCP1 and Ki67 protein levels (*12*). In another small study, analysis of colon adenocarcinoma and adjacent nondiseased tissue from three patient samples indicated a potential link between more malignant colon cancer cells and CDCP1 staining intensity, although a conclusive association could not be demonstrated from such a small cohort (*2*). Noting the presence *in vivo* of CDCP1 shed from the cell surface, these authors proposed that this protein may have utility as a serum marker for colon cancer (*2*). Consistently, analysis of a single patient sample showed an increase of $\sim$2.5-fold in CDCP1 mRNA levels in colon adenocarcinoma compared with adjacent normal tissue, correlating positively with elevated mRNA expression of the current clinical cancer markers carcinoembryonic antigen and epithelial cell adhesion molecule (*11*).

CDCP1 IN HEMATOPOIETIC AND PROGENITOR CELLS

Interestingly, in addition to an association with several solid tumors, CDCP1 may also be an independent marker of leukemia as well as bone marrow and mesenchymal stem/progenitor cells and neural progenitor cells (*13, 15*). Significantly, normal peripheral blood populations, including B and T cells, monocytes, granulocytes, erythrocytes, and thrombocytes, lacked CDCP1 expression (*13*). The lack of complete overlap in expression with current markers of leukemia coupled with the lack of CDCP1 expression by normal cells from peripheral blood indicated that this protein may be useful as an additional marker for diagnosis of leukemia. High CDCP1 expression in colon and breast cancer samples by immunohistochemistry also suggested this protein as a marker for certain epithelial tumors and as a potential target to eliminate tumor cells. However, it was recognized that targeting of CDCP1 in cancer may not only eliminate tumor cells but also adversely affect survival of stem/progenitor cells (*13*).

CDCP1 SUPPORTS CANCER PROGRESSION IN MODEL SYSTEMS

Data supporting a functional role for CDCP1 in cancer progression have come from *in vitro* experiments and animal models. In the first of these reports, Uekita et al. identified tyrosine phosphorylated CDCP1 as a SFK-binding protein in human lung cancer cell lines (*6*). In these cells, phosphorylated CDCP1 was required to overcome anoikis and permit *in vitro* anchorage-independent growth. Importantly, although reduction of CDCP1 in A549 lung cancer cells by RNA interference had no effect on primary tumor growth in mice, metastasis of these cells to lung after tail vein injection was significantly reduced (*6*). Supporting the suggestion that CDCP1 has a role in cancer progression, a more recent study from this group demonstrated that CDCP1 promoted invasion and peritoneal dissemination in mice of gastric cancer cell lines (*14*). The authors proposed that CDCP1 mediates these processes through regulation of cell migration and anchorage-independent growth and suggested that suppression of CDCP1 phosphorylation may be useful for modulating cancer metastasis.

The notion that CDCP1 can be targeted to disrupt cancer processes has recently been tested using an anti-CDCP1 monoclonal antibody generated from a phage displayed combinatorial antibody library (*16*). *In vitro*, this antibody inhibited prostate cancer PC-3 cell migration and invasion (*17*). In addition, when either directly conjugated to the cytotoxin saporin or used in conjunction with species appropriate saporin-conjugated secondary antibodies, anti-CDCP1 antibodies induced PC-3 cell death *in vitro*. Furthermore, intravenously administered saporin-conjugated anti-CDCP1 antibody inhibited subcutaneous growth of PC-3 cells in mice, while both subcutaneous and intravenous delivery of this antibody–cytotoxin conjugate inhibited metastasis of these cells to lymph nodes (*17*). Although encouraging that targeting of CDCP1 can be employed to eliminate cancer cells, to some extent the ability of a toxin-conjugated antibody to induce the death of cells expressing the cognate cell surface antigen is not surprising. It will be of significant interest to determine whether other antibodies that functionally target CDCP1 or, potentially, components of CDCP1 mediated pathways can block cancer progression by directly inhibiting the function of CDCP1.

OPPORTUNITIES AND CHALLENGES IN TARGETING CDCP1 IN CANCER

These reports indicate that overexpression of CDCP1 increases the tumorigenic and metastatic abilities of tumor cell lines in model systems and that targeting of this molecule can inhibit cancer dissemination in these settings. With clear evidence of upregulation of CDCP1 in lung (*1, 9*) and kidney (*10*) cancers, and to a lesser extent in breast cancer (*1, 12*) along with indications of dysregulated expression in colon cancer (*1, 2, 11*), it is likely that aberrant CDCP1 expression facilitates cancer progression in humans. Accordingly, targeting of CDCP1 in these settings may represent a rationale approach to treat certain tumors. However, a key issue potentially hampering this approach is the wide expression of this molecule in normal tissues. For example, CDCP1 mRNA has been detected in a range of organs, including skeletal muscle, colon, kidney, small intestine, placenta, lung, stomach, esophagus, and rectum (*1, 2*), while CDCP1 protein has been described in normal epithelial cells of the colon (*2*), lung, and pancreas, renal tubular subsets, liver hepatocytes (*17*), epidermis (*18*), primary cultures of foreskin keratinocytes (*3*), cells of hematopoietic lineages, and mesenchymal and neural progenitor cells (*13, 15*). In contrast, microvascular endothelial cells and fibroblasts do not express CDCP1 (*2*). Accordingly, as recognized previously (*13*), targeting of CDCP1 in cancer may not only eliminate tumor cells but also adversely impact on the survival of normal cells. However, this problem is certainly not insurmountable as there are small molecule and monoclonal antibody anticancer drugs targeting widely expressed proteins that are generally well tolerated (*19, 20*). These proteins include epidermal growth factor receptors targeted in colon, lung, and head and neck cancers and the human epidermal growth factor receptor-2 (HER-2) in breast and other cancers (*21*). Of relevance, HER-2 has been detected in skin, breast, and placenta as well as in epithelial cells of the gastrointestinal, respiratory, reproductive, and urinary tracts (*22*) and has been detected on subsets of hematopoietic cells (*23*) and also functions in muscle (*24*).

Complementing the *in vitro* and animal-based studies focused on understanding the role of CDCP1 in cancer progression, two recent reports have begun to examine epigenetic events leading to dysregulated expression of the *CDCP1* gene. From these studies it appears that *CDCDP1* expression is inversely correlated with CpG methylation. For example, Ikeda et al. demonstrated that CDCP1 mRNA levels are inversely correlated in 14 cell lines from a range of cancers (leukemia, mastocytoma, colon, breast, and prostate) with the methylation status of 36 CpG motifs spanning the transcription initiation site of the encoding gene. This report also showed a strong inverse correlation between CDCP1 mRNA levels and methylation at these sites in 25 breast cancer samples (*11*). Looking more closely at hematopoietic cell lines, this group showed that CDCP1 mRNA expression in K562 and Jurkat cells is also inversely correlated to CpG methylation (*25*). Further work is required to understand the epigenetic events leading to dysregulated CDCP1 expression. Of course, in addition to the possibility that elevated CDCP1 expression, mediated by epigenetic changes, facilitates cancer, there is also the potential that genetic changes in the *CDCP1* gene (e.g., amino acid altering polymorphisms) will have a role in cancer progression. This suggestion could be verified by *CDCP1* gene analysis of large cohorts of patient samples and matched controls.

If CDCP1 or CDCP1-mediated signaling pathways are to be targets for cancer therapy, a significant challenge is to understand how interactions with other proteins regulate its function. The potential complexity of this task is indicated from the reports summarized earlier that CDCP1-interacting proteins include signaling molecules (SFKs and PKCδ), cell/cell adhesion proteins (N- and P-cadherin), cell/matrix adhesion proteins (syndecan-1 and -4), the tetraspanin CD9, and the serine protease MT-SP1. These proteins are summarized in Fig. 3 which also highlights the changes in SFK-mediated phosphorylation of CDCP1 and PKCδ binding that occur during cell deadhesion and adhesion. The actions of SFKs (*26*), PKCδ (*27*), cadherins (*28, 29*), syndecans (*30*), and certain tetraspanins (*31*) are well known to be important in the aberrant cell adhesion and deadhesion events characteristic of various stages of cancer progression. It also appears that dysregulated MT-SP1 is important in these processes as this protease increases the ability of cell lines derived from a number of cancers to invade though matrix components (*32*). Thus, located on the cell surface CDCP1 may represent a key point of molecular convergence in cell adhesion/deadhesion that could be targeted to disrupt these processes and thereby inhibit cancer progression.

CONCLUSION

In summary, CDCP1 is a cell surface glycoprotein dysregulated in several cancers with potential as a target for cancer treatment. Further work is required to delineate cancers and cancer subtypes which may benefit from targeting CDCP1 or associated proteins. It is also essential that the natural ligand(s) and physiological role of this protein be defined by using, for example, gene deletion studies in mice. A critical issue is to understand how CDCP1 interactions with other proteins and processing of CDCP1 impact cell signaling in cancer and normal physiology.

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