

REVIEW ARTICLE

The role of CDCP1 (CUB domain-containing protein 1) and ADAM12 (a disintegrin and metalloproteinase 12) in ovarian cancer

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Summary

Ovarian cancer (OC) is the second most common gynecological cancer and the deadliest in industrialized countries, with poor outcomes that indicate an urgent need to provide a greater insight into the molecular mechanisms underlying OC. Insights into the complex tumor microenvironment show that besides tumor islets, OC biomarkers can derive from newly formed blood vessels that have endothelial cells with a different molecular signature in comparison with

their normal counterparts. In this view, recent research has been able to highlight promising candidates such as CDCP1 and ADAM12. Our present review summarises their implications in cancer progression with a focus on OC.

Key words: ADAM12, CDCP1, ovarian cancer, tumor microenvironment, tumor progression

Introduction

OC is the second most common gynecological cancer and the deadliest in industrialized countries, with survival rates that have remained unchanged despite recent advancements [1].

Poor outcomes indicate an urgent need to provide a greater insight into the molecular mechanisms underlying OC, to develop improved diagnostic and prognostic biomarkers, guiding treatment protocols, and helping the development of targeted therapies [2,3]. Angiogenesis, as part of the tumor microenvironment, has been validated in clinical trials as a potential target, so far with modest benefits in patient outcome and research still in progress [4,5].

Insights into the complex tumor microenvironment show that besides tumor islets, OC biomarkers can derive from newly formed blood vessels

that have endothelial cells with a different molecular signature in comparison with their normal counterparts [6].

It is known that tumor vasculature offers new possibilities for diagnosis and therapy through its gene expression that is different from the normal vasculature.

A recent high throughput approach on tumor vascular markers in OC, has been able to highlight novel genes with transmembrane localised protein products that could represent promising candidates such as CDCP1 and ADAM12, with an average expression significantly higher in tumors [7].

Our present review summarises CDCP1 and ADAM12 implications in cancer progression with a focus on ovarian malignancy, highlighting their

utility as prognostic biomarkers. In our search, full length articles published between 2000-2014 in Web of Science and PubMed were retrieved using the following search words: "CDCP1", "ADAM12", "cancer", "ovarian", "angiogenesis", "endothelial", "biomarker", "prognosis". Relevant articles found within the cited bibliography were also retrieved.

CDCP1

CUB domain-containing protein 1 (CDCP1) was first identified as a novel gene overexpressed in lung and colon cancer [8], also known as transmembrane and associated with src kinases (TRASK) [9], subtractive immunization associated 135 kDa protein (SIMA135) [10], gp140 [11] or CD318.

CDCP1 is a 836 amino acid, type I transmembrane protein that consists of a signal peptide of 29 amino acids, a larger extracellular domain of 636 amino acids, heavily glycosylated with three regions that have a low homology to C1r/C1s, urchin embryonic growth factor, and bone morphogenetic protein 1 (CUB) domains, a transmembrane and a cytoplasmic domain of 21 and 150 amino acids, respectively [8-10].

The cytoplasmic domain includes five conserved tyrosine residues that act as a substrate of Src Family Kinases (SFK) such as Src, Fyn and Yes for subsequent phosphorylation. This leads to the formation of a multiprotein complex consisting in SFK, protein kinase C δ (PKC δ) and CDCP1, the latter acting as a scaffold structure for two important kinases, and indicates a functional role in tumor cell metastasis [9,10,12,13]. More recently, it has been demonstrated that following plasmin-induced cleavage of the extracellular domain of full length 135 kDa CDCP1 leads to tyrosine phosphorylation of the membrane-retained 70 kDa fragment with subsequent formation the SFK:PKC δ :CDCP1 multiprotein complex. The 65 kDa proteolytic shed ectodomain could represent an alternative signalling pathway, with subsequent molecular functions and could also serve as a serum biomarker, consistent with immunohistochemical positive stainings within the lumen of colonic crypts [14]. In line with this view, CDCP1 was investigated as a suitable biomarker for serum detection in OC due to its expression on the tumor vascular endothelium. There was an increasing difference in CDCP1 serum levels in patients with normal, benign, and malignant ovarian pathology as demonstrated in a relatively small cohort [7].

Membrane-type serine protease 1 (MT-SP1),

which is upregulated in many other cancers including OC, was identified as one of the serine proteases responsible for CDCP1 cleavage [9,14]. As part of the intracellular CDCP1 signaling axis, downstream activation of the pro-survival molecule Akt and Akt-induced tumor cell colonisation has been observed, that is frequently detected in OC and can be targeted to disrupt tumor progression [15,16].

In several studies, high CDCP1 expression in tumor tissues has been linked to a decreased recurrence and/or overall survival in pancreatic [17], renal [18,19] and lung [20] cancer. However, in two papers low levels of CDCP1 have been linked to a poor patient outcome in endometrial adenocarcinoma [21] and esophageal squamous cell carcinoma [22]. In a recent publication that analyzed conflicting survival curves of CDCP1 expression level in various tumor localisations using public databases it was emphasized that CDCP1 function might vary among different malignancies and demands a more careful analysis [22].

Investigating Oncomine Cancer Profiling Database and the Gene Expression Omnibus repository Emerling et al. showed that a significant overexpression of CDCP1 in at least three autonomous microarray datasets is found in OC among other malignancies such as bladder, breast, colorectal, kidney, and pancreatic carcinomas in comparison with their corresponding normal tissues [23].

In a recent paper, Dong et al., investigated epidermal growth factor (EGF)/epidermal growth factor receptor (EGFR) signaling axis as a possible modulator of CDCP1 expression in OC cell lines due to their common role as promoters in cell migration [24]. They reported that following EGF/EGFR activation, the RAS/RAF/MEK/ERK pathway is responsible for CDCP1 increased expression and localisation in the cellular projections of migrating cells, highlighting CDCP1 as a possible target in cancers resistant to anti-EGFR therapy. In the authors' opinion, besides SFK phosphorylation, the EGF/EGFR axis was the third reported modulating mechanism, possibly converging with the second previously described mechanism in renal cancer involving the stabilisation of hypoxia-inducible factors [19]. Similarly, use of tumor conditioned media (TCM) generated under hypoxic conditions in HUVEC cultured cells lead to a greater upregulation of CDCP1 mRNA expression than in cells cultured with normoxic TCM [7]. In a recent report activator protein 1 (AP-1) was suggested as a potential link between CDCP1 overexpression and the RAS/ERK pathway due to its enhancement by ERK activity and by the fact that the promoter

Table 1. CDCP1 investigated tissue expression in different types of cancer

CDCP1 localization	First author [Ref]
Bladder	Emerling et al.[23]
Breast	Bhatt et al.[9], He et al.[14], Sawada et al.[22], Emerling et al.[23]
Cervix	He et al.[14]
Colon and rectum	Scherl-Mostageer et al.[8], Sawada et al.[22], Emerling et al.[23]
Endometrium	Mamat et al.[21]
Esophagus	Sawada et al.[22]
Kidney	Awakura et al.[18], Razorenova et al.[19], Emerling et al.[23]
Lung	Scherl-Mostageer et al.[8], Uekita et al.[13], Sawada et al.[22], Uekita et al.[25], Lin et al.[26]
Ovary	Sasaroli et al.[7], Emerling et al.[23], Dong et al.[24], Harrington et al.[28]
Pancreas	Miyazawa et al.[17], Emerling et al.[23]
Prostate	He et al.[14], Casar et al.[15]
Skin	Hooper et al.[10]

region of CDCP1 contains three complementary docking sites for AP-1, thus mediating the metastatic traits of the RAS/ERK signaling axis [25].

Assessment of data demonstrating that tissue plasminogen activator mediates CDCP1 cleavage in a lung cancer metastasis model validated *in vitro*, *in vivo* and in clinical samples [26] as well as another report in which a high presurgical plasma concentration of tissue plasminogen activator is an independent factor for decreased overall survival in patients with OC [27] could suggest an important role for CDCP1 in OC progression.

Recent evidence shows that CDCP1 was overexpressed in 74% of high grade serous OC, as evaluated through immunohistochemistry and absent in normal ovarian tissue. Experimental downregulation of CDCP1 leads to a reduced cell migration *in vitro* and the use of a targeted anti-CDCP1 monoclonal antibody in a patient derived xenograft significantly reduced tumor burden *in vivo* [28].

The available literature data regarding the CDCP1 investigated tissue expression in different types of cancer is presented in Table 1.

ADAM12

ADAM12 is part of a family of type I transmembrane proteins that include a disintegrin and a metalloproteinase domain expressed in all animal organisms in their structure [29]. ADAMs have been associated with a variety of physiological processes in embryogenesis and in pathological conditions such as various malignancies, inflammatory conditions, rheumatoid arthritis and Alzheimer's disease. Following the same structure

of ADAM proteins, ADAM12 includes the subsequent sequence of domains, beginning with the extracellular N-terminus end: a signal peptide, a pro-domain that retains the metalloproteinase domain inactive until processing, a zinc-dependent metalloproteinase domain, a disintegrin domain, a cysteine-rich domain, an epidermal growth factor like domain, a transmembrane domain and an intracellular tail [29]. As an active protease, ADAM12 has been implicated in the EGFR and insulin-like growth factor signaling. Furthermore, its role in cancer cell dissemination could be attributed to functions in cell adhesion through syndecans that trigger $\beta 1$ integrin-dependent mesenchymal cell spreading [30]. The intracellular domain of ADAM12 seems to play a role in transmitting two-way cellular signals over the cellular membrane. ADAM12 contains several binding sites for the SH3 domain-containing proteins, and interactions with the c-Src tyrosine kinase have been demonstrated [31].

ADAM12, through alternative splicing, is found in two forms, ADAM12-L, a membrane anchored form, and ADAM12-S, a secreted form, lacking the transmembrane and cytoplasmic domains. Its expression has been found upregulated in several malignancies such as breast, colon, lung and gastric carcinomas in comparison with normal tissues through immunohistochemistry and reverse transcriptase-polymerase chain reaction [32]. Increased amounts of ADAM12 have been detected in bladder cancer, and the mRNA level correlated with disease status, decreased after surgery and increased when the tumor relapsed [33].

Overexpression of ADAM12 has also been highlighted in hepatocellular carcinomas and liver metastases from colorectal cancers in contrast to benign focal nodular hyperplasia and normal liver at the mRNA level [34]. In the same study, ADAM12 mRNA and protein expression have been shown to be significantly upregulated by TGF- β in culture conditions, probably through PI3K and ERK1/2 pathways [34].

A study that included 71 patients with breast cancer and 46 women in the control group showed that urine levels of ADAM12 significantly increased with tumor stage and that gelatin, type IV collagen and fibronectin as members of the extracellular matrix can represent substrates for ADAM12 proteolysis, suggesting its role in neoplastic disease progression and matrix plasticity. It has also been postulated that the proteolytic activity could influence certain growth factors such as IGF and HB-EGF that are known to contribute to the progression of neoplastic processes [35]. In particular, activated GPCR stimulates the proteolytic activity of ADAM12 through Eve-1, leading to ectodomain shedding of the membrane-bound form of proHB-EGF, resulting in a soluble molecule capable of EGFR transactivation in an autocrine or paracrine manner [36]. Further research showed that ADAM12 exhibits a differential effect, increasing tumor cell resistance to apoptosis while increasing apoptosis in stromal cells in breast carcinoma [37].

Investigating the known EGFR signaling pathway in human glioblastomas, it was demonstrated that membrane anchored ADAM12 is selectively overexpressed and correlated with proliferation activity, thus suggesting its role in EGFR activation through shed HB-EGF [38].

Interestingly, in a study where anti-ADAM12 antibodies were incubated with gastric cancer cell lines, 4 out of 5 cell lines exhibited an increased proliferative effect, probably through activation of Src family kinases, known to bind the intracellular SH3 binding motif of ADAM12 [39].

EGFR is known to have an important role in tumorigenesis and studies assessing its overexpression in OC have reported a prevalence of 30-98%, affecting progression free and overall survival. The intracellular cascade of events triggered by EGFR activation are correlated with cellular hyperplasia, dissemination, angiogenesis and apoptosis resistance [40] by at least 5 different pathways (PI3K/Akt, Ras/p44/42/MAPK, MEKK/p38 MAPK, PLC/PKC, Rho-GEF/RhoA) [41]. EGFR targeted therapy in OC, either by monoclonal an-

tibodies or tyrosine kinase inhibitors, has been investigated in several phase I/II clinical trials with modest results in an unselected patient cohort, indicating the need for a future personalised translational approach [40].

In OC patients, increased levels of lysophosphatidic acid (LPA) have been detected in the intraperitoneal fluid and have been postulated to play an important role in tumor progression. LPA is generated from membrane substrates by phospholipases and is recognized as a potent mitogen involved in cell cycle progression and its effects are mediated by specific LPA G-protein coupled receptor. The key ligand responsible for EGFR activation in OC was recognized as HB-EGF following LPA-induced proteolysis of pro-HB-EGF [42]. Multiple positive feedback loops were suggested in the same study involving EGFR activation in OC cells leading to augmented transcription and shedding of HB-EGF and increased phospholipase activity contributing to an increased production of LPA, that finally activates EGFR by HB-EGF shedding.

In another study involving 108 patients with OC or normal ovaries, HB-EGF levels were significantly increased in advanced tumor stage in comparison with normal ovaries and its expression significantly correlated with progression free survival. mRNA expression for ADAM 9,10,12 and 17 was evaluated. ADAM12 showed increasing values for mRNA expression index of 7.84 ± 11.49 , 18.1 ± 37.7 , 23.0 ± 39.0 in normal ovary (n=40), OC stage I-II (n=26) and OC stage III-IV (n=42), respectively, but not significantly. However, there was a significant correlation between mRNA expression indices for ADAM12 and HB-EGF [43].

A HB-EGF neutralizing antibody, Y-142, showed a superior *in vitro* neutralizing activity of cell proliferation and angiogenesis in SK-OV-3 OC cell line in comparison with cetuximab and bevacizumab and could have the potential to be implemented into selected targeted therapies [44].

In a comprehensive review of ADAM12, opportunities for targeting ADAM12 have been highlighted. The catalytic domain could be targeted by synthetic protease inhibitors, mutated TIMP endogenous inhibitors or function blocking antibodies and the ADAM prodomain could also play an interesting role while the other domains of ADAM12 could also represent attractive targets [45]. Investigating an OC dormancy and recurrence model in two OC cell lines, it was determined that the anti-angiogenic TIMP3 gene was overexpressed during dormancy and diminished

Table 2. ADAM12 investigated tissue expression in different types of cancer

ADAM12 localization	First author [Ref]
Bladder	Frohlich et al.[33]
Brain	Kodama et al.[38]
Breast	Iba et al.[32], Roy et al.[35], Kveiborg et al.[37], Frohlich et al.[49]
Colon	Iba et al.[32], Le Pabic et al.[34]
Stomach	Iba et al.[32], Carl-McGrath et al.[39]
Liver	Le Pabic et al.[34]
Lung	Iba et al.[32]
Ovary	Sasaroli et al.[7], Serio et al.[41], Tanaka et al.[43], Lu et al.[48]

during recurring growth through an epigenetic mechanism [46], providing evidence for its role as a possible therapeutic modulator.

The role of the tumor microenvironment as a critical player in neoangiogenesis and OC progression started to be explored only in the last few years, due to its potential as a therapeutic target, given its relative genetic stability [47]. The expression of ADAM12 has largely been evaluated within tumor cells. The tumor microenvironment represents an important element in cancer expression and within the few studies that evaluated stromal expression of ADAM12 some inconsistencies have been reported, indicating that stromal expression could depend on the examined tissues and/or species [31].

A study that examined gene expression differences in purified endothelial cells from 10 fresh tissue samples of stage III/IV invasive serous OC and 5 normal ovaries defined a specific gene expression signature in which ADAM12 was up-regulated 7.6-fold in OC specimens in comparison with normal ovary [48].

ADAM12 has also been shown to be expressed in tumor-related vessels of breast cancer specimens in comparison with negative results in normal breast tissue. In the same study it was demonstrated that ADAM12 mediates proteolysis

of endothelial specific substrates such as Tie-2 and VE-cadherin with potential implications in neoangiogenesis and tumor cell migration through the vessel wall [49].

Table 2 displays published data regarding the ADAM12 investigated tissue expression in different types of cancer.

Conclusion

Our review summarizes the available literature data regarding two transmembrane proteins with multiple pathway interactions, within the OC microenvironment. CDCP1 is a regulator of cell metastasis and invasion, while overexpression of ADAM12 has also been shown to promote tumor growth and progression, with successful attempts of targeted inhibition in experimental settings. Additional work is required to better characterize their role as prognostic biomarkers and possible targets for personalized molecular therapy.

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