Exploring the interactions of integrins and CEACAM6 (Review)

AISHA AL-KHINJI

College of Medicine, Qatar University, P.O. Box 2713, Doha, Qatar

Received March 20, 2025; Accepted August 29, 2025

DOI: 10.3892/etm.2025.12986

Abstract. Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive cancer types, and is characterized by rapid progression, resistance to therapy and poor overall prognosis. Adhesion molecules can influence signal transduction, survival, pathogenesis, development and progression in PDAC. However, the role of adhesion molecules and therapeutic targets in PDAC is inadequately characterized. Therefore, the present review critically evaluated the interactions, associations and co-expression patterns of adhesion molecules in PDAC. The interaction between adhesion molecules, such as carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) and integrins, can influence the differentiation, activation, proliferation, metastasis and cytoskeletal remodeling of cancer cells. In addition, adhesion molecules can regulate tumor progression, metastasis, and cellular adhesion and signaling. The present analysis has brought to attention the interaction between CEACAM6 and integrins, which may affect the prognosis of PDAC. Functional and molecular evaluation revealed that CEACAM6 contributes to resistance to anoikis in PDAC through interactions with partner proteins and activation of survival signaling pathways, particularly the Src/focal adhesion kinase axis. In conclusion, the interaction between CEACAM6 and integrins can influence PDAC progression, desmoplasia and treatment resistance. Targeting this adhesion signaling axis presents a promising strategy to improve diagnostic precision and develop more effective personalized therapies for PDAC.

Contents

Correspondence to: Dr Aisha Al-Khinji, College of Medicine, Qatar University, University Street, P.O. Box 2713, Doha, Qatar
E-mail: aalkhinji@qu.edu.qa

Key words: pancreatic ductal adenocarcinoma, carcinoembryonic antigen-related cell adhesion molecule 6, integrins, adhesion molecules, tumor microenvironment, metastasis, extracellular matrix, signal transduction, cancer progression, targeted therapy

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common and aggressive form of pancreatic cancer, accounting for 85% of all PDAC cases and representing the seventh leading cause of cancer globally (1,2). While PDAC predominantly arises from the ductal epithelium of the pancreas, accumulating evidence indicates that acinar cells can also undergo acinar-to-ductal metaplasia and subsequently give rise to PDAC. It is characterized by rapid progression and resistance to therapy, with a 5-year survival rate of ~10% (3). PDAC is frequently diagnosed too late due to heterogeneity in clinical presentation with high metastatic potential, making PDAC the third most common cause of cancer-associated mortality in the USA (4,5).

PDAC is associated with poor prognosis due to a lack of diagnostic biomarkers, a fibrotic tumor microenvironment, desmoplasia, and resistance to chemotherapy and immunotherapy (3,6). Additionally, variability in CA19-9, including absent expression levels in a subset of patients, elevation in benign conditions and inconsistent secretion by tumors, reduces its reliability as a prognostic marker. These limitations hinder early detection and accurate disease monitoring, thereby contributing to delayed diagnosis and ultimately poor prognosis, which restricts its clinical utility for screening asymptomatic patients (7,8). PDAC management poses notable challenges due to a stroma rich in hyaluronan, adhesion molecules, cancer-associated fibroblasts (CAFs) and MMPs, which promote disease progression and drug resistance (9).

A previous study has highlighted the role of cell adhesion molecules, including CEA-related cell adhesion molecules (CEACAMs), in cell-cell and cell-matrix interactions whilst regulating tumor survival, invasion, metastasis, drug resistance and progression of PDAC (10). CEACAMs and integrins can modulate tumor progression through epithelial-mesenchymal transition (EMT), immune evasion and anoikis resistance (11). Understanding the mechanisms and function of adhesion molecules in the fibrotic and

immunosuppressive microenvironment of PDAC is essential for the development of novel therapeutic targets in PDAC management. The present review provides an updated and PDAC-specific summary, highlighting recent mechanistic insights and therapeutic perspectives.

2. Adhesion molecules can facilitate PDAC progression

Adhesion molecules, which are frequently upregulated in cancer, enable tumor cell adhesion, invasion and migration by activating signals that regulate differentiation, the cell cycle and survival (12,13). These features render adhesion molecules potential focal nodes for diagnosis and therapeutic intervention.

Adhesion molecules typically exhibit unique characteristics. Unlike numerous adhesion molecules that signal through direct intracellular interactions through transmembrane and cytoplasmic domains, CEACAM6, a glycosylphosphatidylinositol (GPI)-anchored glycoprotein of the immunoglobulin (Ig) superfamily, lacks both a transmembrane and cytoplasmic domain (14-16). This enables CEACAM6 to mediate cell-cell and cell-matrix adhesion through lateral associations with lipid rafts and co-receptors, promoting PDAC progression (17). Additionally, it can facilitate tumor cell invasion, motility and signal transduction, thereby contributing to tumor growth and metastasis processes in solid malignancies, including colorectal, breast and gastric cancer (16-20).

CEACAM6 expression varies across different stages of tumorigenesis, and is modulated by components of the tumor microenvironment, including collagen, laminin and fibrin (14,16). However, the dynamic and transient membrane association of CEACAM6, particularly its localization within lipid rafts and its status as a GPI-anchored protein lacking an intrinsic signaling domain, hampers precise delineation of its downstream signaling mechanisms (21). CEACAM6 is a key target in PDAC due to its upregulation in the disease, promoting resistance to anoikis, invasion, metastasis and therapy resistance, and it is readily accessible as a GPI-anchored cell surface protein, making it an attractive therapeutic target (17,22). Nevertheless, it is also essential to understand the roles of integrins and other adhesion molecules in the management of PDAC (17-22).

Integrins serve a crucial role in cell communication, tissue regulation and maintenance (23). In addition, integrins facilitate tumor progression by mediating interactions between extracellular matrix (ECM) proteins and cytoplasmic components, potentially influencing the tumor microenvironment (13,16). Therefore, understanding the role of integrins in PDAC is crucial for developing targeted therapies, managing cancer spread, and optimizing patient outcomes (Fig. 1).

The present review aims to critically analyze the oncogenic role of CEACAM6 in PDAC and the mechanisms by which integrins influs to synthesize evidence on the association between CEACAMs and integrins in PDAC, focusing on their co-expression, cross-talk in signaling pathways and combined impact on tumor progression, invasion and therapy resistance. The review further discusses how this interplay highlights the potential for developing targeted therapeutic strategies against these adhesion molecules (Fig. 1).

3. CEACAMs contribute to PDAC progression

Ig superfamily and CEACAMs in PDAC. Ig cell adhesion molecules (IgCAMs), including calcium-independent glycoproteins, such as CEA, constitute a large family of cell surface glycoproteins specializing in cell-cell adhesion (24). CEA, along with other associated IgCAMs or proteins, are involved in homotypic and heterotypic interactions, constituting essential diagnostic markers for various solid tumors, such as colorectal cancer (25).

The human CEA family consists of 29 genes, 12 of which are classified within the CEACAM subgroup (CEACAM1, CEACAM3, CEACAM4, CEACAM5, CEACAM6, CEACAM7, CEACAM8, CEACAM16, CEACAM18, CEACAM19, CEACAM20 and CEACAM21), which cluster on the long arm of chromosome 19 (26). Amongst these, CEACAM1, CEACAM3, CEACAM4, CEACAM6, CEACAM7 and CEACAM8 differ in their Ig-like domain composition, glycosylation patterns, membrane anchoring mechanisms and tissue distribution (Fig. 2) (27,28). Structurally, CEACAMs share an N-terminal Ig variable (IgV)-like domain followed by constant-like domains (A and B), with extensive glycosylation accounting for ≤50% of the molecular mass of the protein (29).

In addition, these proteins are bound to the cell membrane by either a GPI moiety (CEACAM5, CEACAM6, CEACAM7, CEACAM8, CEACAM16 and CEACAM18) or a proteinaceous transmembrane region (CEACAM1, CEACAM3, CEACAM4, CEACAM19, CEACAM20 and CEACAM21) (Fig. 2) (25,30,31). This structural diversity influences the functional roles of the CEACAM subtypes in adhesion, migration and immune modulation in cancer. However, limited expression of certain CEACAMs in animals limits their mechanistic investigations (24,32,33). For example, CEACAM5 and CEACAM6 are highly expressed in humans but absent in mice, while CEACAM7 and CEACAM8 also lack murine orthologs, thereby limiting their *in vivo* study potential (24,32,33).

CEACAM1. CEACAM1 has a cytoplasmic tail that harbors immunoreceptor tyrosine-based inhibition motifs (ITIMs), which are critical for intracellular signaling (34), and has a molecular weight of ~90 kDa (35). Another feature of CEACAM1 is the IgV domain that facilitates homophilic and heterophilic adhesion through complementarity-determining regions (CDR)-like loops, whilst ITIM phosphorylation recruits Src homology region 2 domain-containing phosphatase (SHP)-1 (also known as PTPN6) and SHP-2 (also known as PTPN11), thereby inhibiting T-cell signaling and supporting immune evasion (34,36). Previous studies have shown that CEACAM1 is involved in bidirectional signaling, modulating immune checkpoint regulation and tumor progression (28,37). However, it remains under investigation as a prognostic marker target in PDAC, melanoma, colorectal cancer and non-small cell lung cancer, and as an emerging immunotherapeutic target across multiple malignancies (28,37). However, its clinical relevance in PDAC specifically remains under investigation (38,39).

CEACAM5. CEACAM5, has one IgV domain and six IgC2 domains (arranged as A1-B1-A2-B2-A3-B3) and a GPI moiety

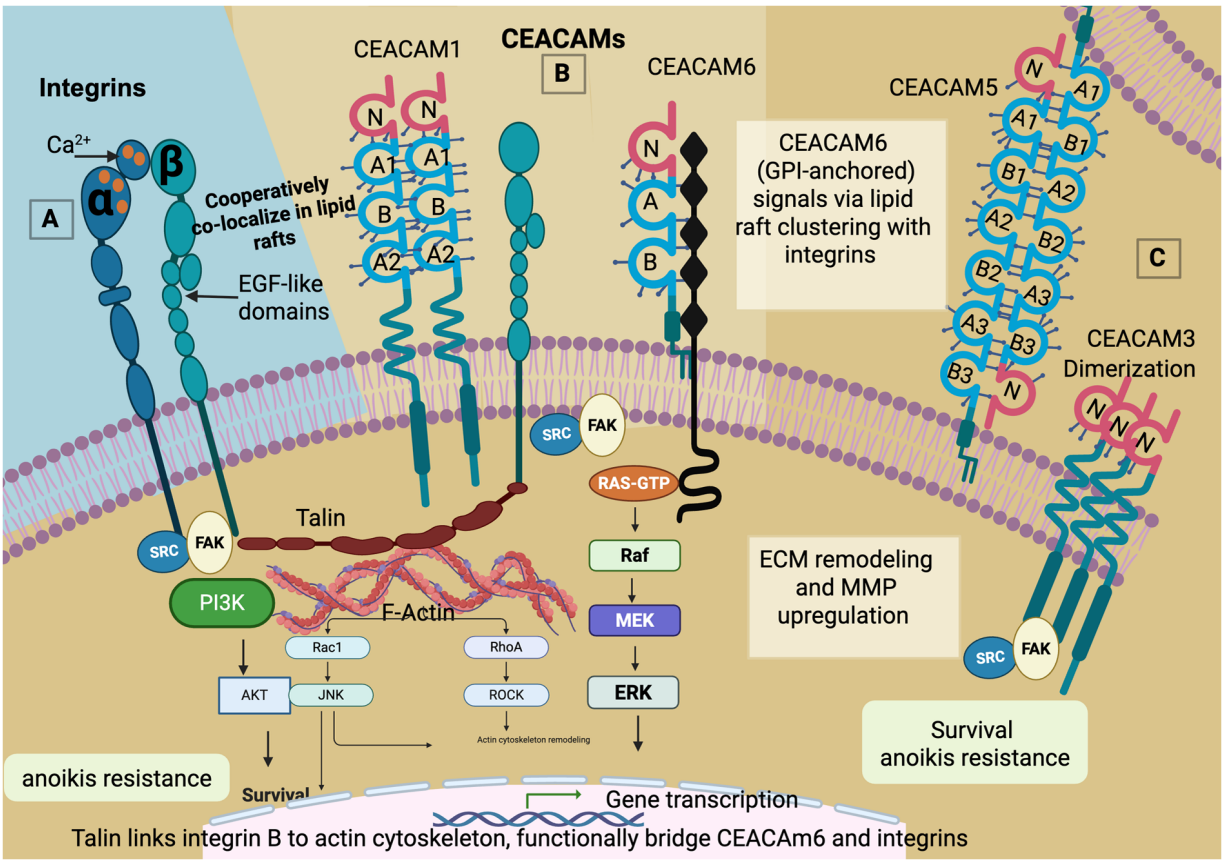

Figure 1. Integrin and CEACAM adhesion receptors in pancreatic ductal adenocarcinoma. (A) Integrin (left) receptors with a cytoplasmic domain contain α and β subunits with EGF-like and calcium-binding domains, which link to intracellular signaling via talin and focal adhesion kinase (FAK), and (B) CEACAMs with either a transmembrane receptor anchored by glycosylphosphatidylinositol on the cell surface, such as CEACAM6 and CEACAM5, or (C) CEACAM receptors with a cytoplasmic domain, such as CEACAM1 and CEACAM3. Talin is illustrated as a cytoskeletal adaptor protein that connects integrins to the actin cytoskeleton and, functionally, to CEACAM-associated signaling hubs. While direct binding of CEACAMs to talin has not been fully demonstrated, CEACAMs and integrins co-localize in lipid rafts, enabling shared downstream signaling via Src/FAK and PI3K/Akt pathways. CEACAM, carcinoembryonic antigen-related cell adhesion molecule; FAK, focal adhesion kinase; RhoA, Ras homolog family member A; ROCK, Rho associated protein kinase.

anchored to the cell membrane (40,41). Furthermore, it has a molecular weight of 180-200 kDa with extensive N-linked glycosylation (18,42). CEACAM5 mediates cell-cell adhesion through its IgV domain and is likely involved in signaling cascades due to its lipid raft localization (16). By associating with transmembrane receptors, such as integrins (α5β1, αvβ3), CEACAM1 and EGFR, CEACAM5 can influence downstream signaling, thereby supporting metastatic spread and immune evasion (43,44). Therefore, CEACAM5 has been proposed to be a possible serum biomarker and target in PDAC immunotherapy in clinical settings (20,43,45).

CEACAM6. CEACAM6 (also known as CD66c) comprises an N-terminal IgV domain and two IgC2 domains (A1-B1), forming a compact three-domain structure that is anchored to the membrane by a GPI anchor (29). With a molecular weight of 90-95 kDa, CEACAM6 is heavily glycosylated and frequently localizes to lipid rafts (28,46). CEACAM6 lacks a cytoplasmic domain but can facilitate signal transduction through interactions with various integrin co-receptors, such as α5β1 and αvβ3, to activate key pathways, including the focal adhesion kinase (FAK), Src and PI3K/Akt pathways (16,21,47). Studies have previously demonstrated that CEACAM6 can promote tumor cell survival, anoikis resistance and EMT, whilst also contributing to chemoresistance in pancreatic, colorectal and breast cancer (16,18-20,22,48). Through indirect interactions with ECM components, such as fibronectin and vitronectin, CEACAM6 can also serve a pivotal role in PDAC invasion and progression (48).

CEACAM7. CEACAM7 consists of an N-terminal IgV domain and two IgC2 domains (A1-B1), with a GPI anchor facilitating membrane association (21), and has a molecular weight of 75-85 kDa (43). Whilst CEACAM7 is generally considered to be a tumor suppressor in normal epithelial tissues, it displays oncogenic properties in PDAC (25,49,50). CEACAM7 mediates both homophilic and heterophilic adhesion, including interactions with CEACAM6 and integrins, and is involved in lipid raft-associated signal transduction (49). In addition, CEACAM7 has been implicated in peritoneal metastasis, is enriched in cancer stem cell populations, and is a potential early diagnostic and prognostic marker in PDAC (50). However, the therapeutic relevance of CEACAM7 is currently under investigation, including its applications in chimeric antigen receptor (CAR)-T cell therapy (50).

Integrated structure-function. Within the CEACAM family, the IgV domain is a highly conserved structural feature that

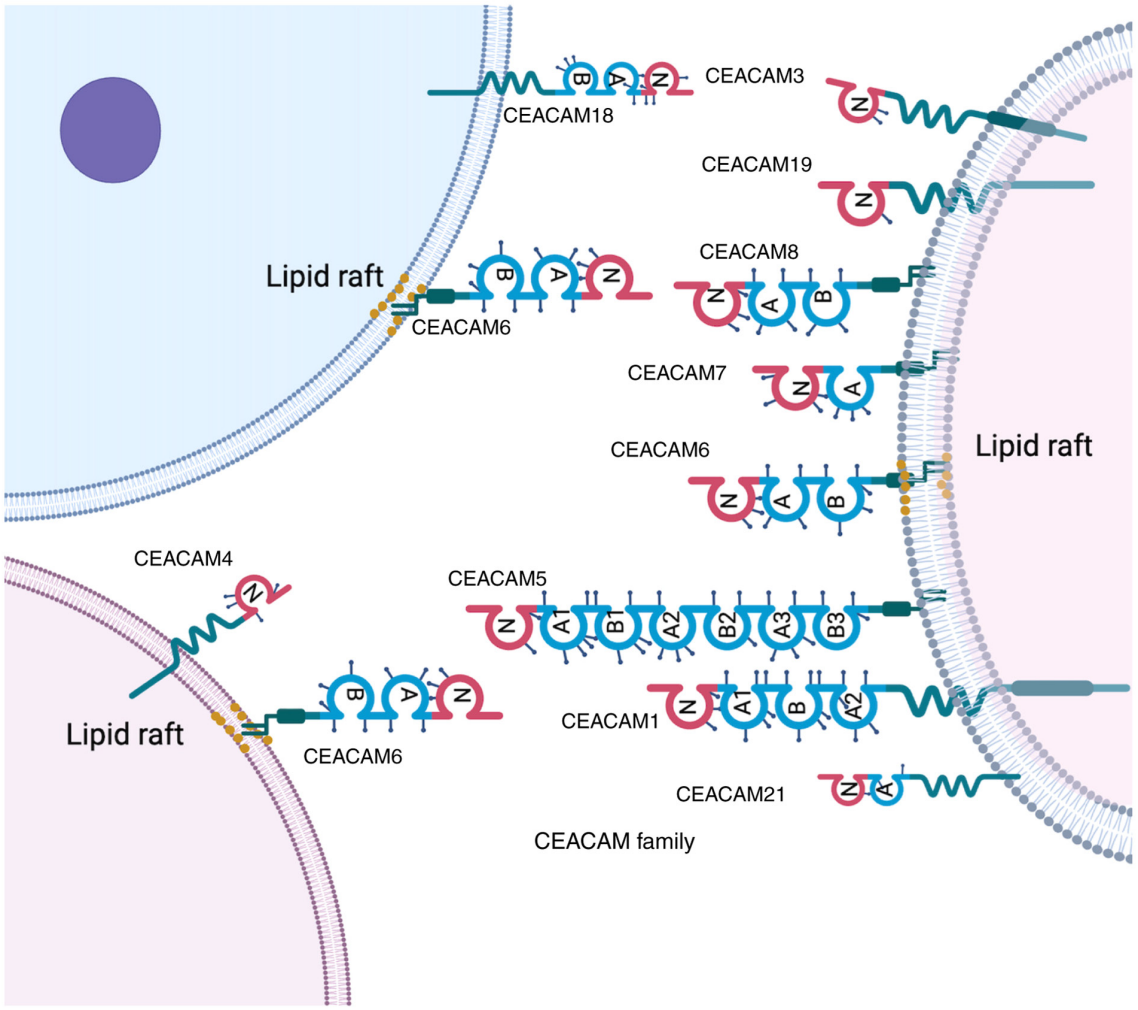

Figure 2. A selection of human CEACAM family members showing different CEACAM structures. CEACAM5, CEACAM6, CEACAM7, and CEACAM8 lack transmembrane and cytosolic domains, while CEACAM1 is anchored through transmembrane domains. The blue spheres represent constant domains depicted by A and B. The red spheres are the variable N-terminal Ig variable-like domain. CEACAM, carcinoembryonic antigen-related cell adhesion molecule.

provides adhesive functions through β-sandwich folds and a CDR-like loop structure (51). However the type of membrane anchoring varies, with CEACAM1 incorporating a transmembrane helix allowing direct intracellular signaling, whereas CEACAM5, CEACAM6 and CEACAM7 are GPI-anchored, facilitating dynamic lipid raft localization and co-receptor engagement (21,52). By contrast, glycosylation of CEACAM family members influences protein folding, stability and protease resistance, thereby contributing to the functional plasticity in tumorigenesis (29,53).

The IgV domain provides opportunities for antibody-mediated blockade, since ITIM motifs can be exploited for immune modulation, whereas GPI anchors may be targeted to disrupt membrane clustering (54). Furthermore, the unique structural attributes of each CEACAM molecule are associated with their distinct roles in PDAC pathobiology (17,29,53), offering a framework for biomarker development and personalized treatment strategies.

CEACAMs are upregulated in PDAC. Members of the CEACAM family, particularly CEACAM1, CEACAM5, CEACAM6 and CEACAM7, have emerged as key markers of the pathogenesis of PDAC, influencing diagnosis, prognosis and therapy (14,53). CEACAM1 has a cytoplasmic tail containing ITIMs (55) and is frequently upregulated in PDAC, where it has been proposed as both a clinical biomarker and a therapeutic target (38-58). CEACAM1 modulates immune responses through co-inhibitory functions, particularly by inhibiting T-cell receptor signaling through SHP-1/2 recruitment, making CEACAM1 a promising target in immunotherapy (28). However, previous studies have reported conflicting findings, with CEACAM1 being expressed at lower levels in the tumors of patients with PDAC compared with in normal pancreatic tissues (59,60). Furthermore, the roles of CEACAM1 in tumorigenesis and cancer progression have been inconclusively reported, highlighting the need for further mechanistic studies (61). CEACAM1 is upregulated in PDAC tissues and patient serum, and its increased levels are associated with tumor stage and progression, supporting its potential as a diagnostic and prognostic biomarker (58). In addition, it has been evaluated as a non-invasive serum marker (58), with elevated CEACAM1 first reported in the serum of patients with PDAC. Simeone *et al* (57) further demonstrated that combining CEACAM1 with CA19-9 significantly improved sensitivity and specificity for early-stage PDAC detection. Furthermore, tissue-based assays revealed

that CEACAM1 expression can distinguish PDAC from chronic pancreatitis and normal pancreatic tissue, supporting its role as both a serum and tissue biomarker (57,62). By contrast, high-CEACAM1 expression is associated with tumor grade, metastatic potential and patient survival, with functional divergence between isoforms. Specifically, isoform CEACAM1-L generally suppresses tumor progression through ITIM-mediated signaling, whereas isoform CEACAM1-S, lacking ITIM, is often upregulated and linked to oncogenic behavior (39,62).

Through ITIM-mediated recruitment of SHP-1 and SHP-2 phosphatases, CEACAM1 can downregulate T-cell receptor signaling, thereby facilitating tumor immune escape (63). In addition, CEACAM1 promotes can tumor angiogenesis through VEGFR2 pathway activation, thereby offering opportunities for anti-angiogenic combination therapies with synergistic potential (59,64).

Monoclonal antibodies neutralizing the inhibitory effects of CEACAM1 have been assessed, whereas bispecific antibodies that can target CEACAM1 alongside other checkpoints, such as TIM3, and small-molecule inhibitors of its downstream signaling components, including SHP2 inhibitors, Src/FAK inhibitors and PI3K/Akt or MAPK pathway inhibitors, are actively under investigation (54,65). Emerging strategies utilizing CEACAM1-directed CAR-T cell therapies that exploit its tumor-specific expression profile to achieve targeted cytotoxicity have also been explored (66,67). Combinatorial approaches, pairing CEACAM1 inhibition with chemotherapy, radiotherapy or co-targeting of integrins, may further enhance therapeutic efficacy by disrupting survival pathways and modifying the tumor microenvironment (54).

Methodological variability, including differences in detection techniques, antibody specificity and scoring criteria, result in heterogeneity in findings on CEACAM1 expression in PDAC (68). Additionally, intratumoral heterogeneity further adds to the complexity, with spatially distinct expression patterns across tumor subclones and stromal niches (53). The tumor microenvironment, including immune cell infiltration, stromal composition and hypoxia, can further influence CEACAM1 expression and function, underscoring the need for context-specific evaluation (69,70).

The multifaceted role of CEACAM1 in PDAC supports its integration into current precision medicine strategies. Understanding of its involvement in immune regulation, angiogenesis and cell adhesion should inform the development of targeted therapies and enable the predictive modeling of treatment outcomes. Therefore, future research should aim to standardize CEACAM1 detection methods, validate its utility in large patient cohorts and elucidate isoform-specific mechanisms of action (70).

Similarly, CEACAM5 is involved in cell adhesion, intracellular signaling, tumor progression and metastasis (71-73). CEACAM5 can mediate function through homophilic (with itself on neighboring cells) and through heterophilic interactions with other CEACAM family members, such as CEACAM6 and CEACAM1 (53). CEACAM5 expression is frequently upregulated in malignancies, including PDAC, where it is localized to tumor cells and fibrotic or necrotic regions (71-75). Associations have been reported between CEACAM5 and immune checkpoint regulation and cancer stemness in PDAC, emphasizing its potential role as a biomarker and therapeutic target (59).

CEACAM7 has been identified as a potential early diagnostic and prognostic marker in PDAC (49). Although considered a tumor suppressor due to its downregulation in several epithelial cancer types, such as colorectal carcinoma, CEACAM7 expression is frequently upregulated in PDAC, especially during early tumorigenesis and in cancer stem cell-enriched populations (20,75). CEACAM7 has also been implicated in peritoneal metastasis through interactions with CEACAM6 and integrin subunit αV (75). Its dual expression profile and targeting in CAR-T cell study highlight its complex but important therapeutic potential (50).

CEACAM6/CD66c is a GPI-anchored glycoprotein with a variable IgV-like domain and two constant domains (A and B), through which CEACAM6 can form both homo- and heterodimers. Initially identified in hematological malignancies, CEACAM6 was later identified as a biomarker for colorectal cancer (17,19,31). CEACAM6 is expressed on epithelial and leukocyte surfaces (30).

In conclusion, CEACAMs exhibit diverse structural features and biological functions that can each influence PDAC development and progression in distinct manners. Their differential expression patterns and interactions with the tumor microenvironment offer potential for advancing early detection strategies and developing targeted therapies.

Pathological role of CEACAM6 in PDAC diagnosis and progression. CEACAM6 expression is upregulated in PDAC, with a previous study showing a 20- to 25-fold increase in adenocarcinoma cells compared with normal pancreatic ductal epithelial cells (17). Upregulation typically begins early in pancreatic tumorigenesis, including in pancreatic intraepithelial neoplasia lesions (1,17), where it is associated with metastasis and poor prognosis (14,16). CEACAM6 has been identified to be a prognostic biomarker independent of KRAS mutation status, and is associated with aggressive PDAC subtypes (14,76).

In addition, CEACAM6 can promote cell migration, invasion and proliferation by upregulating MMPs and cyclin D1/CDK4 (53,77). CEACAM6 can facilitate EMT by promoting loss of epithelial traits and acquisition of mesenchymal characteristics, which is reflected in its inverse correlation with E-cadherin expression and its association with increased expression of mesenchymal markers such as vimentin (73). Mechanistically, miR29 a/b/c directly targets CEACAM6 mRNA, and their downregulation leads to CEACAM6 overexpression, thereby enhancing EMT and invasion (73,74). In addition, CEACAM6 is associated with anoikis (an apoptotic response triggered by detachment from the ECM) resistance primarily through enhanced Akt phosphorylation, which promotes cell survival (47,78). Supporting this, CEACAM6 inhibition has been reported to increase cell susceptibility to caspase-mediated anoikis by reducing Akt phosphorylation (47).

CEACAM6 can support tumor angiogenesis by activating FAK and paxillin signaling, promoting vasculogenic mimicry (79). Anti-CEACAM6 antibodies have been found to reduce MMP9 activity, invasion and angiogenesis (32). Furthermore, upregulation of CEACAM6 expression has

been observed to contribute to gemcitabine chemoresistance, whilst its inhibition sensitized cells to gemcitabine-induced cytotoxicity (80).

Mechanistically, CEACAM6 interacts with ECM components, such as fibronectin, through α5β1 and αvβ3 integrins, thereby enhancing anchorage-independent survival (17,47). These diverse roles, ranging from EMT and immune evasion to chemoresistance and angiogenesis, highlight the role of CEACAM6 in PDAC progression and as a promising therapeutic target (Fig. 3) (81,82).

Role of CEACAM6 in ECM component interactions. CEACAM6 serves a key role in mediating interactions with ECM components, influencing PDAC progression, therapeutic resistance and tumor microenvironment dynamics. Although the majority of the currently known functional insights stem from studies in other malignancies, including lung adenocarcinoma, where CEACAM6 promotes cisplatin resistance and is regulated by miR-146a and miR-26a, the relevance of CEACAM6 to PDAC is becoming increasingly evident (83,84).

In the tumor microenvironment, CEACAM6 can modulate cell adhesion, migration and drug resistance through homotypic and heterotypic cell-cell interactions involving integrin receptors (14,17,45). CEACAM6 activates integrin signaling cascades, particularly those involving α5β1 and αvβ3 integrins, which are known to interact with various ECM components, such as laminin, fibronectin, collagen and hyaluronan (85). These interactions contribute to anchorage-independent survival, EMT and chemoresistance in PDAC (14,17).

A previous study has revealed that CEACAM6 can regulate integrin-mediated signaling through PI3K/Akt activation, which are mechanisms observed in lung and breast cancer and are likely conserved in PDAC (16). By contrast, CEACAM1 has been shown to require tyrosine phosphorylation for interaction with β3 integrin in melanoma, suggesting a broader CEACAM-integrin signaling axis (26,86,87).

Despite evidence of oncogenic roles, including angiogenesis, invasion, resistance to apoptosis and immune evasion, the molecular mechanisms underlying the interaction of CEACAM6 with the ECM and the contribution to desmoplastic remodeling in PDAC remain inadequately characterized (16,73,88-90). CEACAM6 may influence the fibroinflammatory remodeling of the ECM, but this desmoplastic interaction remains underexplored (91). Understanding how CEACAM6 interacts with ECM receptors and regulates PDAC cell behavior is essential. As shown in Fig. 4, STRING-based protein-protein interaction analysis indicates that CEACAM6 is connected with multiple integrin subunits [e.g. ITGA5, ITGA2, ITGB3, integrin β (ITGB)4 and ITGA6], which are key ECM receptors. These predicated and known associations suggest that CEACAM6 may influence integrin-mediated adhesion, signaling and ECM remodeling, thereby supporting its role as both a diagnostic marker and a therapeutic target in PDAC (Fig. 4).

The desmoplastic reaction in PDAC, marked by dense collagen deposition, activation of CAFs and altered ECM composition, is influenced by CEACAM6 (14). GPI-anchored localization to lipid rafts facilitates clustering with integrins α5β1 and αvβ3, promoting adhesion to fibronectin, collagen I and hyaluronan, and forming signaling hubs that amplify matrix deposition and tumor cell survival (16,21). In addition, upregulation of CEACAM6 expression has been found to enhance fibronectin assembly, stimulate collagen cross-linking and stiffen the ECM (17).

CEACAM6 can also support CAF activation through α5β1-mediated FAK/Src signaling and TGF-β feedback, thereby sustaining myofibroblast differentiation (51,92,93). CEACAM6 upregulates MMP-2 and MMP-9 through the NF-κβ pathway and increases tissue inhibitors of MMP expression, thereby altering the proteolytic balance toward ECM accumulation (91). Furthermore, CEACAM6 promotes mechanotransduction through α5β1 and αvβ3 signaling, reinforcing fibrosis through Yes-associated protein/WW domain-containing transcription regulator 1 activation, whilst also driving hyaluronan accumulation and proteoglycan remodeling, all of which elevate interstitial fluid pressure and impair drug delivery (94).

Clinically, CEACAM6-driven desmoplasia can limit therapy efficacy by creating physical and pharmacological barriers (14,95). Future studies should explore the spatial heterogeneity of CEACAM6 expression, identify predictive biomarkers and optimize anti-desmoplastic interventions for PDAC management.

4. Integrin and CEACAM involvement in signaling pathways in PDAC

Integrins are heterodimeric transmembrane receptors consisting of 18 α and 18 β subunits that combine to form 24 distinct integrin receptors (96). The structural architecture of integrin subtypes is directly associated with their functional roles in PDAC progression (75). Structurally, each subunit includes a cytoplasmic tail, a transmembrane domain and a large extracellular region (97). While the β subunits anchor to the actomyosin cytoskeleton and transmit intracellular signals, the α subunits mediate selective binding to ECM proteins, including collagen and laminin (98,99). These subunits coordinate to form functional integrin receptors that engage various ECM glycoproteins, such as collagen, laminins and fibronectin, thereby facilitating bidirectional signaling between tumor cells and their microenvironment (100).

In PDAC, integrin-mediated signaling can activate several oncogenic pathways, including the Ras/MAPK, PI3K/Akt and Rho-GTPase cascades (101,102). ITGB5 expression, which is upregulated by TGF-β signaling in CAFs, has been documented to contribute to tumor growth and metastasis. By contrast, inhibition of TGF-β using LY2157299 in murine models could reduce ITGB5 expression, leading to smaller tumors and improved survival (103,104).

Other integrin subtypes also serve distinct roles in PDAC. Integrin α3 can upregulate the EMT transcription factor zinc finger E-box binding homeobox 1 (ZEB1) and activate JNK, thereby promoting chemoresistance and metastasis (105). ITGB4, which is elevated in PDAC, can also enhance local invasion and metastasis through the MEK1/ERK1/2 cascade and FAK binding (105-108). Although ITGB4 is known to facilitate cell migration and invasion, its precise mechanistic role in PDAC remains to be fully elucidated. The structural basis for ITGB4 activation involves tyrosine phosphorylation at Y1510, which induces conformational

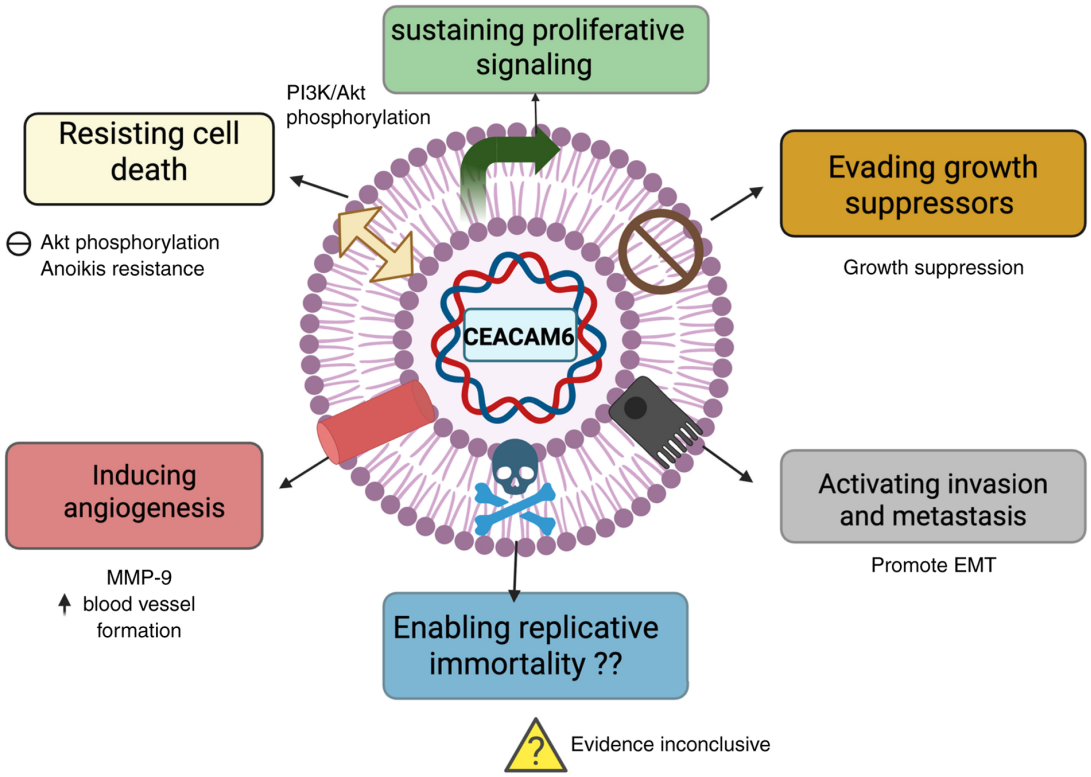

Figure 3. CEACAM6 involvement in six of the cancer hallmarks. CEACAM6 has multiple mechanisms in pancreatic ductal adenocarcinoma and contributes to these biological processes. CEACAM6 sustains proliferation through PI3K/Akt pathways and induces angiogenesis via MMP-9. However, the involvement of CEACAM6 in replicative immortality is inconclusive. CEACAM, carcinoembryonic antigen-related cell adhesion molecule.

changes that facilitate downstream oncogenic signaling and crosstalk with EGFR pathways. ITGB4 engages in crosstalk with EGFR, promoting tumor cell proliferation, drug resistance and signaling interplay central to PDAC pathogenesis (83,109,110).

Beyond the classical integrin subunits, other CEACAM family members, such as CEACAM1, can contribute to integrin-associated signaling in PDAC through their roles in immune modulation, angiogenesis and adhesion regulation (86). CEACAM1 is a valuable clinical biomarker and a promising therapeutic target in pancreatic cancer due to its N-terminal IgV-like domain and ≤3 constant C2-like domains, which enable diverse functional roles in tumor biology (53). CEACAM1 has been found to exhibit immunomodulatory functions, where the structural domains facilitate co-inhibitory activities by inhibiting T-cell receptor signaling through the recruitment of SHP-1 and SHP-2 (87). Importantly, CEACAM1 can also interact with integrins, such as β2 integrins on immune cells and β3 integrins on endothelial cells, thereby influencing adhesion and co-inhibitory signaling (87). CEACAM1 can promote angiogenesis through the VEGFR2 pathway, which may inform the development of anti-angiogenic therapeutic strategies (111).

Despite advances in structural biology, the complete 3D architecture of integrin receptors remains to be fully resolved, particularly the structural basis for integrin signaling. Further research into integrin-CEACAM interactions and downstream signaling mechanisms is essential to understand their role in PDAC progression and therapeutic resistance.

Integrins as facilitators with other proteins in PDAC. Integrins are essential mediators of cell-ECM interactions in PDAC, influencing cell adhesion, migration and intracellular signaling. By binding to specific ECM proteins, integrins initiate signal transduction pathways that regulate cancer progression and therapeutic resistance (112). Certain integrins can also serve as prognostic biomarkers in PDAC, being associated with disease severity and patient outcomes (92,93,111,112). For example, high ITGA2 expression correlates with shorter progression-free and overall survival times, as well as chemoresistance in PDA (113,114).

Integrins engage in signaling crosstalk with numerous growth factors and cytokines, including EGF, insulin growth factor and TGF-β, thereby influencing cellular behavior and ECM remodeling (115,116). ITGB1 can form heterodimers with α2, α4 and α5 subunits to mediate focal adhesions between tumor cells and the ECM (117). By contrast, cytoplasmic proteins, such as talin and kindlin, can regulate ligand affinity and integrin activation by linking integrins to the actin cytoskeleton (113-118). In addition, as illustrated in Fig. 1, talin may also functionally bridge integrins and CEACAMs within adhesion complexes. While direct physical binding between CEACAMs and talin has not been fully demonstrated, experimental evidence supports integrin-CEACAM co-localization and clustering in lipid rafts, which facilitates shared downstream signaling through Src/FAK pathways (16,19,47). This suggests that integrins and CEACAMs may operate with the same adhesion and signaling hubs. Integrins, including ITGB3, can be internalized through clathrin-mediated endocytosis when they are not under high mechanical tension (119,120).

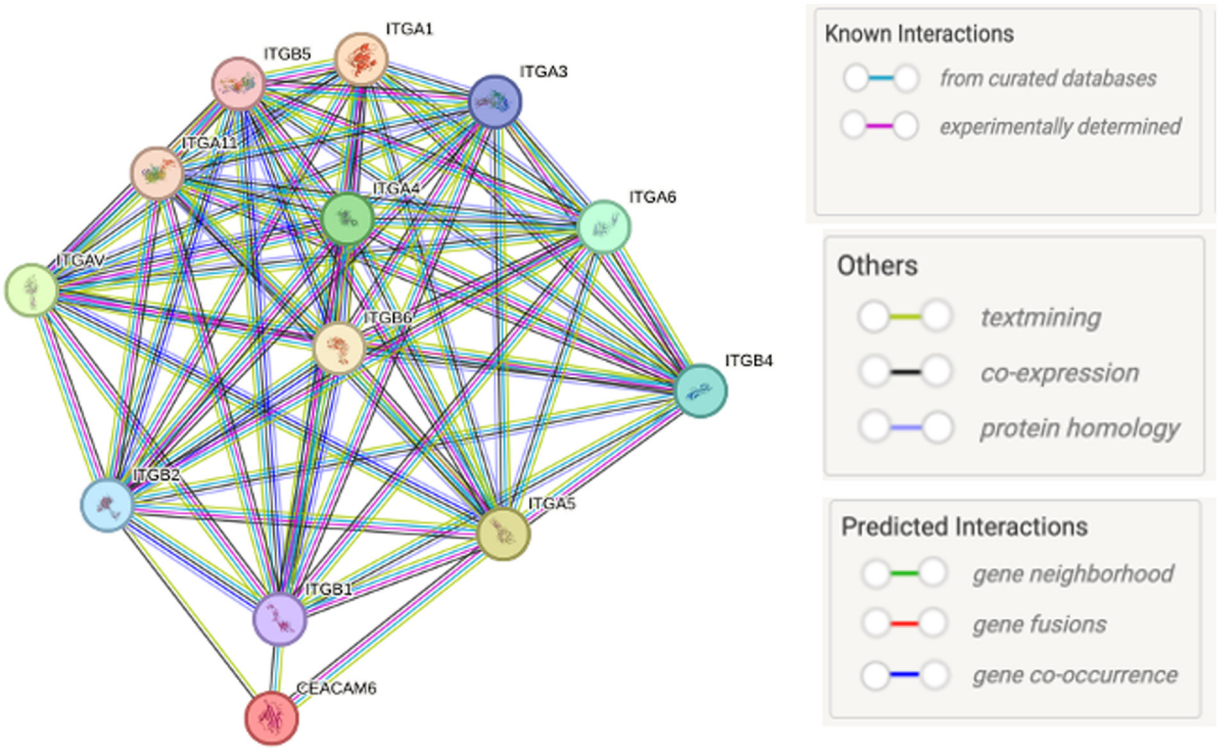

Figure 4. STRING protein-protein network analysis of the relationship between CEACAM6 and integrins. The network was generated using the STRING database (v11.5; https://string-db.org). Lines represent known or predicted associations with the following sources: Curated databases (light blue), experimentally determined (pink), gene neighborhood (green), gene fusions (red), gene co-occurrence (blue), text mining (yellow), co-expression (black) and protein homology (lavender) CEACAM, carcinoembryonic antigen-related cell adhesion molecule; ITG, integrin.

Within the tumor microenvironment, CAFs can drive integrin-mediated desmoplasia (121). Integrin αvβ5 regulates the endocytosis and recycling of active α5β1, which sustains fibronectin matrix assembly and focal adhesion turnover (122). These processes enhance actomyosin contractility and ECM stiffening, thereby activating a fibroblast into myofibroblastic CAF phenotype that maintains ECM remodeling and promotes disease recurrence (121). Similarly, integrin α11β1 can mediate CAF-fibronectin interactions, enhancing PDAC cell migration (122). Integrin α3β1 binds to laminin-111, collagen I and laminin-332 in the ECM, to facilitate PDAC cell motility (123).

Targeting integrins *in vitro* has shown therapeutic potential. Monoclonal antibodies against α11 integrin have been developed to disrupt CAF adhesion to collagen and impair cancer cell invasion (123,124). In 3D models, PDAC cells migrated along fibroblast extensions using α5β1, which adhered to fibronectin deposited by CAFs (124). Integrins αvβ3, α5β1 and αvβ5 are involved in directing tumor invasion and ECM deposition (125). However, the molecular crosstalk between α11β1 and other integrins in PDAC remains poorly characterized.

Integrins can also interact with CEACAMs, co-localizing in lipid rafts where they cluster and modulate signaling. Specifically, CEACAM1 and CEACAM6 have been reported to associate with β1 and β4 integrins, enhancing adhesion and survival pathways in epithelial cancers (19). In PDAC, ITGB4, which influences tumorigenesis, is activated through tyrosine phosphorylation at Y1510, regulating downstream MEK1-ERK1/2 signaling (19,108). In addition, ITGB4 expression has been found to be upregulated in PDAC compared with in normal or inflamed pancreatic tissues (126). Its activation promotes EMT, metastasis and chemoresistance, making ITGB4 a potential prognostic marker (102,127). In gastric cancer, ECM protein 1 promotes metastasis and glycolytic activity through the ITGB4/FAK/SOX2/hypoxia-inducible factor-1α axis, suggesting a conserved oncogenic mechanism (126,127).

Additionally, ZEB1 can directly upregulate ITGA3 and ITGB1 by binding to their promoters, contributing to tumor cell proliferation and migration in PDAC (128). The integration of integrin-mediated signaling with EMT programs and fibroinflammatory remodeling emphasizes their role in tumor aggressiveness. Understanding the function of integrins and their molecular partners in PDAC is essential for the identification of novel therapeutic targets. Table I (74,105,111,129-134). summarizes the various integrins associated with PDAC pathogenesis and their functional roles in PDAC.

Association between integrins and CEACAM6 in PDAC. The interplay between CEACAM6 and integrins contributes to PDAC progression by regulating adhesion, migration and signaling dynamics within the tumor microenvironment (14,17). CEACAM6 mediates both homophilic interactions with other CEA family members and heterophilic interactions with integrins, particularly αvβ3 and α5β1 (16,17). These interactions facilitate cancer cell adhesion, invasion, EMT and resistance to anoikis (73,135,136). These interaction between CEACAM family members and various integrins, supported by both experimental and predictive evidence, are summarized in Table II (50,74,103,129,137,144-167).

CEACAM6 has been implicated in modulating integrin-dependent signaling, particularly through the activation of FAK and c-Src kinase pathways, which enhance integrin affinity for ECM proteins, such as fibronectin and vitronectin (17). In PDAC, CEACAM6 overexpression upregulates the activation state of α5β1 integrins without altering receptor abundance, promoting increased fibronectin binding, matrix assembly, and disruption of normal differentiation and survival mechanisms (139). Furthermore, CEACAM6-integrin crosstalk is not limited to cancer but also can regulate inflammatory and infectious diseases, including the role of CEACAM6 as a receptor for adherent-invasive *E. coli* in Crohn's disease (126), suggesting its functional versatility across pathologies (20,140). CEACAM6 has also been shown to facilitate lipid raft-mediated signaling, supporting uptake mechanisms and the phosphorylation of key downstream effectors, such as Akt and MAPK, through integrin-linked kinase (ILK) activation (141,142).

A previous study has demonstrated that clustering of CEACAM6 on the membrane could promote co-localization with integrin α5β1, which in turn activated the Akt and MAPK signaling cascades. This integration of CEA family proteins with integrin signaling reinforced malignant behaviors, such as enhanced cell-ECM adhesion, increased invasive capacity and survival under anchorage-independent conditions (141). Furthermore, STRING network analysis (Fig. 4) illustrated the functional protein-protein interaction landscape between CEACAM6 and key integrins. Protein-protein interactions were analyzed using the STRING database (version 11.5; https://string-db.org/). The query was performed using Homo sapiens as the organism. Interaction sources included experimental data, curated databases, co-expression, text mining, co-occurrence and homology. The confidence score threshold was set at 0.700 (high confidence). The resulting network was visualized in STRING, and interaction lines were color-coded based on the evidence channel (e.g., experimental, co-expression and text mining).

This bioinformatics representation consolidates experimental evidence and predictive modeling, reinforcing the functional relevance of CEACAM6-integrin networks in PDAC progression.

Mechanistic analysis of CEACAM6-integrin interactions in PDAC. CEACAM6, a GPI-anchored adhesion molecule, clusters within lipid rafts and engages integrin receptors, particularly α5β1 and αvβ3 (47). These interactions enhance integrin avidity for ECM ligands, such as fibronectin and vitronectin, facilitating stable cell-matrix adhesion and initiating downstream signal transduction (17). Upon co-localization with integrins, CEACAM6 promotes the activation of FAK and c-Src, leading to the phosphorylation of ILK and the subsequent activation of the PI3K/Akt and MAPK signaling pathways. This dual activation supports key malignant phenotypes, including sustained proliferation, survival and invasion (47).

CEACAM6 engages integrins, particularly αvβ3 and α5β1, to activate Akt signaling, conferring anoikis resistance under anchorage-independent conditions, a survival effect supported in multiple models, including colorectal, breast, lung and gastric cancer, where CEACAM6-driven upregulation of anti-apoptotic proteins, such as Bcl-2 and survivin (16,51,80,94,136,139). Additionally, CEACAM6 can modulate ECM remodeling by enhancing the expression and activity of MMP-2 and MMP-9, primarily through FAK- and NF-κB-dependent transcriptional regulation. This effect is mediated via its interactions with integrins, particularly α5β1 and αvβ3, which cluster with CEACAM6 in lipid rafts to activate FAK/Src signaling. The resulting upregulation of MMPs facilitates the degradation of the basement membrane, thereby promoting local invasion and metastatic dissemination (17,142).

CEACAM6-integrin signaling also contributes to EMT by downregulating E-cadherin and inducing mesenchymal markers, such as Snail and ZEB1, through the sustained activation of the Akt and MAPK pathways (143,144). These signaling cascades result in resistance to gemcitabine and other chemotherapeutic agents (103,143,144). In addition, CEACAM6-mediated integrin signaling can increase drug efflux and reinforce survival pathways, suppressing apoptotic responses to cytotoxic stress (103). The tumor microenvironment then further modulates CEACAM6-integrin dynamics. Increased matrix stiffness, cytokine gradients and altered ECM composition increase integrin signaling, reinforcing CEACAM6-mediated oncogenic programs in PDAC (103).

5. Therapeutic targeting of CEACAM6 and integrins in PDAC

Current therapeutic strategies. CEACAM6 and integrins are promising targets for the treatment of PDAC due to their roles in tumor adhesion, survival, invasion and chemoresistance (41). Monoclonal antibodies targeting CEACAM6 have exhibited preclinical efficacy by disrupting integrin interactions and downstream signaling pathways, thereby reducing invasion and metastasis (67). Similarly, integrin-specific strategies using α5β1 and αvβ3 inhibitors have been shown to impair tumor-ECM interactions and enhance chemosensitivity (145).

CAR-T therapies targeting CEACAM6 and associated CEACAM family members, such as CEACAM7, represent an emerging immunotherapeutic avenue that can overcome the immunosuppressive microenvironment found in PDAC (146). Combination strategies, pairing CEACAM6/integrin inhibitors with chemotherapy (gemcitabine) or matrix-modulating agents, have exhibited synergistic effects and offer promise in overcoming drug resistance (147).

Clinical trial status and biomarker validation. Early-phase trials of anti-CEACAM6 antibodies and antibody-drug conjugates have reported favorable safety and preliminary efficacy, particularly in patients with high CEACAM6-urpregulated malignancies, such as colorectal and gastric cancers. In PDAC, these agents remain at the preclinical stage, where dual-specificity constructs such as CT109-SN-38 have demonstrated potent cytotoxicity in a pancreatic cancer model (148). Integrin inhibitors, particularly those targeting αvβ3 and α5β1, are currently undergoing phase I/II evaluation in several solid tumors, including melanoma, and lung cancer, where combination regimens generally outperforming monotherapy (149,150). Although clinical data in PDAC remain limited, a preclinical study suggested that the CEACAM6 and

Table I. Different integrins in PDAC and the distinct functional roles.

First author/s, year	Integrin subtype	Mechanism of action	Functional role	(Refs.)
Kemper *et al*, 2021	ITGAV	Mediated by E and P selectin; high expression of ITGAV activates latent TGF-β and upregulates TGF-βR1 through the activity of SMAD4.	Upregulation in selectin deficiency enhances intraperitoneal and pulmonary metastatic PDAC and drives EMT.	(74)
Mia *et al*, 2021	ITGβ1	Binds to TGF-β receptor 2; signals through focal adhesion molecules and upregulates pro-fibrotic signaling.	Promotes tumor growth of PDAC and metastasis through an increase in the expression of fibronectin or vitronectin; associated with poor patient survival.	(131)
Kuninty *et al*, 2019	ITGA5	Modulates TGF-β1/SMAD pathways via focal adhesion kinase pathways.	High ITGA5 in PDAC is associated with poor overall survival; increases desmoplasia, decreases tumor perfusion and contributes to gemcitabine resistance.	(132)
Li *et al*, 2015	ITGβ6	Cytoplasmic domain of ITGβ6 directly binds to ERK2 and increases MAPK activity (101); ITGB6 induces ETS1 phosphorylation in the ETS-ERK-signaling pathway in the upregulation of MMP-9 (102).	Promotes proliferation.	(133)
Schnittert *et al*, 2019	ITGA11	Binds to collagen on the cell surface; Integrin α11 is a receptor of collagen type I and is upregulated by CAFs; the positive correlation between TGF-β indicates that the upregulation of ITGA11 may be attributed to TGF-β, with no clear mechanistic activity.	Promotes cell metastasis and invasion; regulates pancreatic stellate cell differentiation into CAFs.	(129)
Chen *et al*, 2022	ITGA3	Upregulates cytokeratin-19 suppresses T-cell activity. ITGA3 interacts with collagen I and upregulates EGFR signaling via LRIGI induction.	High ITGA3 expression promotes cell invasion and aids tumor cells in evading apoptosis, and its high expression is associated with a poor prognosis in PDAC.	(130)
Humphries *et al*, 2022	α6β4 (ITGA6/ ITGB4)	Interacts with ECM components, such as fibronectin and laminin.	Formation of hemidesmosomes is inhibited, allowing α6β4 to act as a signaling integrin that stimulates tumor progression.	(134)
Masugi *et al*, 2015	ITGβ4	Combines with several oncogenic receptor tyrosine kinases, including c-Met, ErbB1 and ErbB2, to amplify the signaling pathways that accelerate cancer invasion.	Involved in promoting EMT and regulating cancer invasion.	(105)
Cavaco *et al*, 2018	α2β1 (ITGA2/ ITGB1)	Mediates cancer cell adhesion to ECM components.	Promotes strong adhesion of tumor cells to ECM components (e.g., collagen), thereby supporting PDAC progression.	(111)

PDAC, pancreatic ductal adenocarcinoma; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; CAFs, cancer-associated fibroblasts; ITG, integrin; ITGAV, integrin subunit αV; LRIGI, leucine-rich repeats and immunoglobulin-like domains protein 1.

integrin expression levels are associated with treatment response (60). Additionally, CEACAM6-integrin expression profiles may predict chemotherapy sensitivity, supporting the development of personalized treatment approaches (17).

Challenges and limitations. Therapeutic resistance remains an important barrier, mediated by pathway redundancy, tumor heterogeneity and microenvironmental adaptation (151,152). Subclonal variation in CEACAM6/integrin expression may

Table II. Association between different CEACAM members and integrin proteins.

First author/s, year	Association	Integrin protein	CEACAM member	(Refs.)
Brümmer *et al*, 2001	Interaction between integrin β_3 and a fusion protein containing the cytoplasmic domain of CEACAM1; *cis* associations between integrin β_3 and CEACAM1.	β_3	CEACAM1	(166)
Vuijk *et al*, 2020	Co-localization at the cell membrane and highly expressed in pancreatic ductal adenocarcinoma; co-expressed at the cell membrane and diffusely expressed in tumor cells and surrounding fibrosis; co-localization and activation via lipid rafts.	αvβ6; α5β1	CEACAM5	(167)
Kemper *et al*, 2021	CEACAM7 co-localizes with integrin αV in pancreatic ductal adenocarcinoma, facilitating lipid raft–mediated signaling. This interaction enhances ECM remodeling and supports fibrotic progression.	αV	CEACAM7	(74)
Schnittert *et al*, 2018	Integrin αvβ3 expression is upregulated through CEACAM6 cross-links with extracellular matrix proteins, fibronectin and vitronectin. In addition, CEACAM6 co-localizes with integrin α5β1 within the lipid rafts, where Src kinase-mediated activation of α5β1 enhances downstream oncogenic signaling	α5β1; αvβ3	CEACAM6	(129)
Raj *et al*, 2021	Fusion of extracellular Ig variable domain of CEACAM3 and intracellular domain of integrin β1.	β1	CEACAM3	(50)

CEACAM, carcinoembryonic antigen-related cell adhesion molecule.

lead to incomplete responses, whilst upregulation of alternative adhesion molecules can bypass targeted inhibition (153). By contrast, the desmoplastic and immunosuppressive microenvironment of PDAC limits drug delivery and the efficacy of immunotherapy (154,155). Furthermore, variable expression levels and a lack of standardized cut-off values complicate the development of biomarkers (60).

6. Clinical translational applications and future perspectives

Clinical relevance of CEACAM6-integrin interactions. Although several CEACAM family members have been implicated in cancer biology, CEACAM6-integrin interactions hold significant clinical value across early diagnosis, prognosis, treatment selection and disease monitoring in PDAC (17,57). CEACAM6 expression is frequently upregulated, by ≤25-fold, in PDAC tissues and precursor lesions, making it a promising biomarker for early detection (57,75). High CEACAM6 expression levels are also associated with aggressive tumor subtypes and poor survival, serving as an independent prognostic marker regardless of KRAS status (14,60). This enables risk stratification and informed decisions on the use of intensified or experimental therapies and predicts treatment response. Elevated CEACAM6 expression is associated with gemcitabine resistance, whilst specific integrin expression patterns influence chemotherapy outcomes, supporting personalized therapeutic strategies (17,156).

Monitoring of circulating CEACAM6 and integrin-related proteins enables real-time assessment of treatment efficacy, providing a dynamic alternative to traditional imaging methods (17,157). Additionally, the strong association of CEACAM6/integrins with metastasis risk can inform post-treatment surveillance and the planning of adjuvant therapy (60).

Translational challenges and limitations. Translating CEACAM6-integrin research into clinical application faces several key barriers. A major challenge is the lack of assay standardization, with varying methodologies across laboratories hindering reproducibility and cross-study comparison (158,159). Tumor heterogeneity further complicates clinical translation, since the expression of CEACAM6 and integrins varies within and between tumors (14,75). Therefore, single-site biopsies may misrepresent the full molecular landscape, limiting the accuracy of treatment decisions (160).

The dynamic expression of these molecules during disease progression and therapy adds complexity, requiring longitudinal monitoring that may be impractical in routine settings due to cost and infrastructure constraints (47,161,162). Additionally, unfavorable regulatory environments, particularly for advanced therapies, such as CAR-T cell therapies, necessitate specialized clinical trial designs that can prolong the approval process (163,164).

Future clinical applications. CEACAM6-integrin research is essential in transforming PDAC management through precision diagnostics, targeted therapies and real-time monitoring. Molecular profiling of CEACAM6-integrin expression will enable personalized treatment selection, guiding choices of chemotherapy, targeted agents or immunotherapies based on

individual tumor characteristics. By contrast, the emergence of liquid biopsy platforms incorporating CEACAM6-integrin biomarkers, such as circulating tumor cells, extracellular vesicles and soluble proteins, offers a non-invasive method for monitoring disease progression and treatment response, allowing dynamic, real-time clinical decision-making (166,167).

Integrating CEACAM6-integrin targeting with immunotherapy or oncolytic virus platforms represents a compelling strategy to enhance antitumor immune responses by modulating the tumor microenvironment. In addition, the relevance of CEACAM6-integrin signaling across multiple tumor types suggests the potential for pan-cancer therapeutic strategies.

7. Discussion

The present review aimed to highlight the crucial role of CEACAM6-integrin crosstalk in the pathogenesis of PDAC. CEACAM6, a GPI-anchored adhesion molecule, is frequently upregulated in PDAC, which contributes to tumor cell survival, immune evasion, chemoresistance and desmoplastic remodeling (14,17). Through lipid raft-mediated clustering, CEACAM6 co-localizes with integrins, particularly α5β1 and αvβ3, amplifying downstream oncogenic signaling through the FAK, Src, PI3K/Akt and MAPK pathways (47,48).

The CEACAM6-integrin axis facilitates anchorage-independent survival, EMT, matrix stiffening and CAF activation, which are hallmarks of PDAC aggressiveness. These interactions also contribute to resistance to chemotherapy by altering drug uptake and activating anti-apoptotic signaling pathways. CEACAM6-integrin co-expression serves as a prognostic marker and may guide personalized therapy. High CEACAM6 levels are associated with poor survival and gemcitabine resistance, whilst integrin profiles predict responsiveness to combination therapies. Despite promising therapeutic targets, pathway redundancy, tumor heterogeneity and assay standardization make PDAC management challenging.

Therapeutic strategies combining anti-CEACAM6 agents with integrin inhibitors, matrix-degrading enzymes or immunotherapies show synergistic potential. Additionally, there is a need to consider integrating CEACAM6-integrin biomarkers into clinical workflows through liquid biopsy approaches, such as blood-based assays of circulating tumor cells, extracellular vesicles or circulating tumor DNA (156-160). Future studies should explore isoform-specific functions, protein-protein interactions and temporal expression changes across disease stages. Mechanistic insights into CEACAM6-integrin signaling and its impact on ECM remodeling will be crucial for designing next-generation precision therapies in PDAC.

In conclusion, CEACAM6 and integrins represent critical regulators of PDAC progression through their influence on adhesion, survival signaling, desmoplasia and immune modulation. Their interactions activate oncogenic pathways, such as the FAK, PI3K/Akt and MAPK pathways, thereby enhancing tumor invasion, metastasis and therapeutic resistance. The lipid raft-mediated clustering of CEACAM6 with integrins, such as α5β1 and αvβ3, reinforces ECM remodeling, chemoresistance and anchorage-independent survival, whilst integrins themselves contribute to EMT, angiogenesis and immune evasion. These molecules shape a tumor microenvironment that is conducive to malignancy and hinders the effectiveness of therapy.

CEACAM6-integrin dynamics are essential in precision oncology in PDAC, ranging from biomarker-driven diagnostics to targeted therapies. Integrating molecular profiling with emerging treatments, such as CAR-T cells, bispecific antibodies and matrix-disruptive strategies, may overcome current limitations posed by tumor heterogeneity, signaling redundancy, and stromal barriers.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

AAK was responsible for conceptualization, literature review, drafting, writing, critical revision and final approval of the manuscript. Data authentication is not applicable. The author has read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares they have no competing interests.

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