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REVIEW

Pancreatic cancer stem cell markers and exosomes - the incentive push

Sarah Heiler, Zhe Wang, Margot Zöller

Sarah Heiler, Zhe Wang, Margot Zöller, Tumor Cell Biology, University Hospital of Surgery, D 69120 Heidelberg, Germany

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Correspondence to: Dr. Margot Zöller, Tumor Cell Biology, University Hospital of Surgery, Im Neuenheimer Feld 365, D 69120 Heidelberg, Germany. m.zoeller@uni-hd.de
Telephone: +49-6210-565146
Fax: +49-6210-565199

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Abstract

Pancreatic cancer (PaCa) has the highest death rate and incidence is increasing. Poor prognosis is due to late diagnosis and early metastatic spread, which is ascribed to a minor population of so called cancer stem cells (CSC) within the mass of the primary tumor. CSC are defined by biological features, which they share with adult stem cells like longevity, rare cell division, the capacity for self renewal, differentiation, drug resistance and the requirement for a niche. CSC can also be identified by sets of markers, which for pancreatic CSC (Pa-CSC) include CD44v6, c-Met, Tspan8, alpha6beta4, CXCR4, CD133, EpCAM and claudin7. The functional relevance of CSC markers is still disputed. We hypothesize that Pa-CSC markers play a decisive role in tumor progression. This is fostered by the location in glycolipid-enriched membrane domains, which function as signaling platform and support connectivity of the individual Pa-CSC markers. Outside-in signaling supports apoptosis resistance, stem cell gene expression and tumor suppressor gene repression as well as miRNA transcription and silencing. Pa-CSC markers also contribute to motility and invasiveness. By ligand binding host cells are triggered towards creating a milieu supporting Pa-CSC maintenance. Furthermore, CSC markers contribute to the generation, loading and delivery of exosomes, whereby CSC gain the capacity for a cell-cell contact independent crosstalk with the host and neighboring non-CSC. This allows Pa-CSC exosomes (TEX) to reprogram neighboring non-CSC towards epithelial mesenchymal transition and to stimulate host cells towards preparing a niche for metastasizing tumor cells. Finally, TEX communicate with the matrix to support tumor cell motility, invasion and homing. We will discuss the possibility that CSC markers are the initial trigger for these processes and what is the special contribution of CSC-TEX.

Key words: Pancreatic cancer; Cancer stem cells; Stem cell markers; Exosomes; Crosstalk

Core tip: Cancer progression relies on a small population of cancer stem cells (CSC), characterized by longevity, self renewal, drug resistance and requirement of a niche. In addition, CSC abundantly deliver exosomes (TEX) allowing CSC a long distance communication. At the descriptive level, CSC are characterized by a set of so called CSC markers. We here discuss for pancreatic cancer that the CSC markers CD44v6, c-Met, Tspan8, alpha6beta4, EpCAM, claudin7, CXCR4 and prominin1 can in a concerted activity account for all CSC features. This includes CSC TEX activity due to the engagement of CSC markers in TEX biogenesis and enrichment in TEX.

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INTRODUCTION

Pancreatic cancer (PaCa) has a dismal prognosis due to late diagnosis and early metastatic spread. Thus, there is an urgent need for improving diagnosis and for a better understanding of the mechanisms underlying PaCa progression. We briefly outline the state of the art in concern about diagnosis with emphasis on tumor exosomes (TEX) as a promising diagnostic tool and proceed to introduce cancer stem cells (CSC) including the processes of epithelial mesenchymal transition (EMT) and premetastatic niche formation. After introducing exosomes, we outline the functional activity of Pa-CSC markers and how they contribute to the dismal prognosis of PaCa.

Pancreatic cancer diagnosis

PaCa still holds the highest mortality rate, which is due to late diagnosis, early metastatic spread and drug and chemoresistance[1]. Though the survival rate of patients with a tumor of < 1 cm is close to 100% and about 50% fo patients with a tumor of < 2 cm survive, the 5-year survival rate for locally advanced PaCa is 9% and for metastatic PaCa 2%[2], which is very demanding for approaching early diagnosis[3-9].

Imaging advices (computed tomography, endoscopic ultrasound, emission tomography and combined computed tomography/positron emission tomography) are well established for therapy control. These new imaging advices have strongly improved PaCa detection, yet are still suboptimal for early detection[3]. Therefore, imaging is frequently combined with additional serum biomarkers. The most common marker, carbohydrate-associated antigen 19-9 (CA19-9) is helpful in response monitoring and in taking a decision on resectability, but shows insufficient sensitivity and specificity for early PaCa detection[10]. Thus, the search for additional biomarkers is still ongoing[11]. To name a few, mucin 1 (Muc-1), which is also detected in other malignancies, showed a minor improvement compared to CA19-9[12]. It is suggested to be suited for early stage detection[13]. DJ-1 (Parkinsonism associated deglycase) and combinations of regenerating family member 1β, syncoilin, anterior gradient 2 with CA19-9 improve sensitivity and specificity[14,15]. A serum proteome analysis of patients with PaCa showed significant upregulation of 40 proteins. Several of these proteins revealed disease associations to TP53[16,17]. In addition, upregulation of galectin-1, gelsolin, lumican, 14-3-3σ, cathepsin D, cofilin, moesin and plectin were described in PaCa patients. Gelsolin and lumican were suggested as markers to differentiate PaCa from chronic pancreatitis (CP)[18-20]. The search for early serum PaCa markers also includes genetic and epigenetic markers[21-23]. DNA methylation of basonuclin and ADAM metalloproteinase with thrombospondin type 1 motif 1 (ADAMTS1) in serum indicate prognostic valence[24]. Recovery of hypermethylated TNFR superfamily member 10c, and apoptotic chromatin condensation inducer 1[25] and of long noncoding (lnc) RNA metastasis associated lung adenomcarcinoma transcript 1 are predictors of poor survival[26]. Recovery of miR-21, miR-210, miR-155 and miR-196a in the serum allows differentiating PaCa patients from healthy donors. Recovery of these miRNA correlates with PaCa progression[27]. When combining the evaluation of CA19-9, miR-155, miR-181a/b and miR-196a stage I PaCa could be detected and differentiated from CP[28]. Serum miR-20a, miR-21, miR-24, miR-25, miR-99a, miR-185 and miR-191 allowed to differentiate PaCa from CP patients and healthy donors[29]. A panel of 10 free serum miRNA indicated discrimination between tumor stages[30]. A statistical meta-analysis confirmed free serum miRNA as a diagnostic tool in PaCa. However, none of these miRNA are selective for PaCa[31]. Recently, TEX in serum, which allow concomitantly evaluating PaCa-promoted genetic, epigenetic, lipidomic and proteomic alterations[23], received increased interest. A first report based on mutations in KRAS and TP53 revealed promising results[32]. Another study reports on the recovery of miR-17-5p and miR-21 in serum TEX. Recovery of miR-17-5p and miR-21 in serum exosomes differs between PaCa and CP patients and correlates with tumor progression[33]. The finding that glypican-1$^+$ can be detected with 100% specificity and 100% sensitivity in serum TEX of PaCa patients attracted much attention. Notably, this included reliable detection of PanIN (pancreatic cancer *in situ*). Furthermore, the level of glypican-1$^+$ TEX correlated with tumor burden and survival time. A mouse model with specific KRAS mutations promoting spontaneous PaCa development, confirmed recovery of glypican-1$^+$ TEX at the stage of intraepithelial lesions[34]. We were concerned about the recovery of Pa-CSC protein markers (CD44v6,

Tspan8, EpCAM, β4 integrin) in serum TEX. Additionally, microarray screenings of PaCa serum and tumor line derived TEX suggested a panel of miR-1246, miR-4644, miR-3976, miR-4306 to be suited for PaCa diagnosis. Two findings should be mentioned. TEX-enclosed miRNA is recovered at a significantly higher level than free serum miRNA. Second, we recommend to evaluate both protein and miRNA markers, which improved sensitivity (100%) and specificity (80%)[35].

These few studies on serum TEX require large scale controls. Yet, results so far appear promising for the long awaited early diagnosis of PaCa, where late diagnosis of PaCa becomes particularly vicious due to the early spread of PaCa[36]. To shed light on the unexpected power of TEX, we introduce CSC including the process of epithelial mesenchymal transition (EMT) and the establishment of a premetastatic niche in advance of reasoning on the suggested linkage between Pa-CSC markers, TEX and tumor progression.

Cancer stem cells and the epithelial mesenchymal transition

The propensity to metastasize relies on the small subpopulation of CSC, named according to several joint features with embryonic and adult SC[37]. CSC are long lived, can self renew and differentiate, slowly progress through the cell cycle, are radiation and drug resistant and account for primary tumor growth and metastatic spread[38]. CSC and ESC share several signaling pathways, particularly over-expression of Oct4 (POU class5 homeobox1), Nanog (Nanog homeobox) and avian myelocytomatosis viral oncogene homolog (c-Myc)[39] and signaling *via* Notch, Wnt and Hedgehog[40], frequently initiating activation of the Ras-Raf-MAPK and PI3K-Akt pathway[41].

The metastatic cascade of epithelial tumors is initiated through EMT[42,43]. EMT essentially depends on CSC[44,45]. The hallmarks of EMT are loss of cell-cell adhesion, *via* E-cadherin downregulation and gain in motility by remodeling of the cytoskeleton and formation of new cell-substrate contacts supported by intermediate filament proteins like vimentin[43]. Initiation of the EMT program depends on a multitude of signals received from the environment that activate a corresponding array of intracellular signaling cascades[46-48], which force expression of EMT transcription factors Twist, Snail, Slug, Zeb1 and others[49]. Transforming growth factor (TGF)β is the major EMT inducer[50], which signals through its receptors phosphorylating SMAD2 and SMAD3 that bind to SMAD4, the complex translocating to the nucleus[50,51]. Wnt signals activate β-catenin that support Snail, but also vimentin transcription[52-54]. Activation of the EMT program through receptor tyrosine kinase (RTK) ligands like HGF, EGF, FGF and PDGF (hepatocyte-, epidermal, -fibroblast, -platelet-derived growth factor), appears to be content dependent[55-57].

EMT is initiated by downregulation of E-cadherin at the transcriptional and posttranscriptional level. EMT transcription factors are recruited to the E-cadherin promoter and repress transcription[58]. Histone modifying enzymes cooperate in E-cadherin promoter repression. This includes polycomb group proteins, which form polycomb repressive complexes silencing transcription *via* modifying histones and recruiting additional repressors[59]. Another important factor is Bmi1 that is upregulated in CSC and supposed to facilitate the EMT phenotype. Bmi1 downregulates Pten, which leads to activation of the PI3K/Akt pathway and posttranslational stabilization of Snail[60]. Furthermore, Twist can bind to the Bmi1 promoter and upregulate its expression[61]. Histone deacetylases are also engaged in E-cadherin silencing. They are either recruited by Snail[62] or by Twist directly associated with the histone deacetylase complex[63]. MiRNA presents the second major epigenetic mechanism engaged in the EMT process. In most instances miRNA binds to the untranslated region of their target genes, which prohibits target gene translation[64]. The engagement of miRNA in EMT was first described for the miR-200 family. This family comprises miR-200a/b/c, miR-141 and miR-429. Decreased expression of the miR-200 family is accompanied by enhanced Zeb1 and Zeb2 expression[65]. Additional miRNAs regulating EMT transcription factors are miR-29b, miR-30a, miR-205[66-68]. Other EMT targets of miRNAs are E-cadherin (miR-9), N-cadherin (miR-194), Nestin and Star1 (miR-661), pulmonary adenoma resistance 3 (miR-491-5p), which is engaged in tight junction (TJ) distortion and p120 (catenin δ1) (miR-197)[69-73]. Notably, some miRNA concomitantly regulate CSC and EMT. miR-200c becomes activated *via* p53, which binds to the miRNA promoter. As a consequence tumorigenicity and metastasis are suppressed[74,75]. Also, by depletion of miR-21 the number of CSC decreases and EMT is reverted[76]. In this context, it is important to remember that in epithelial cancer the process of EMT is transient[77]. In line with this, the epithelial phenotype can be restored by a double-negative feedback loop, between Zeb, Snail1 and Gata3 and miR34a or miR-200[78,79]. A similar feedback loop was described for miR-203 and Snail1[80].

There is some debate, whether non-CSC by turning into the mesenchymal phenotype acquire CSC features or whether CSC transfer the required messages towards non-CSC[44]. These options may not be mutually exclusive, taking the vision that CSC initiate the EMT phenotype in non-CSC, either by activating relevant signaling cascades by direct cell contact or *via* TEX, which could account for both binding initiated activation of signaling cascades and transfer of genetic and epigenetic information. The latter option has been most convincing demonstrated for the preparation of the premetastatic niche by CSC TEX.

Cancer stem cell niches and exosomes

CSC share with embryonic and adult SC dependence on a crosstalk with a special surrounding, called niche[81,82]. Adult SC and CSC niches, which are important to maintain stemness, consist of epithelial and mesenchymal cells and extracellular substrates[83]. An important contributor in the CSC niche are cancer-associated fibroblasts (CAF). CAF provide HGF, interleukin (IL)6, PDGFβ, prostaglandins (PG) and proteases, which jointly remodel the extracellular matrix (ECM)[84,85]. Other important players are mesenchymal stem cells (MSC)[86], which cooperate with CAF and macrophages (Mϕ)[87]. MSC are stimulated by tumor cell-derived IL1 to secrete PGE2, which operates in an autocrine manner promoting cytokine secretion and induces β-catenin signaling. These signaling cascades promote CSC conversion of adjacent non-CSC tumor cells[88]. Stroma cell-derived tumor necrosis factor (TNF)α and IL6 sustain TGFβ production and attract MSC to produce CSC supportive CXCL7[89]. Tumor-derived growth factors stimulate resident fibroblasts to secrete fibronectin promoting CSC attachment. Stromal fibroblasts- and CAF-derived CXCL12 (stroma-derived factor 1, SDF1) attracts CXCR4 expressing hematopoietic, endothelial cell progenitors and CSC[90]. c-Met becomes involved *via* HGF expressing MSC and β-catenin that together with the Tcf/Lef (lymphoid enhancer binding factor 1) complex translocates to the nucleus and initiate transcription of cell cycle related genes like *cyclin D1* and *c-Myc*[91]. Activated integrin-linked kinase (ILK) further supports nuclear translocation of β-catenin, where ILK activation is promoted by matrix-bound β1 integrins and costimulatory signals from the environment[92]. Finally, there is evidence that niche maintenance is supported by a mutual exchange of miRNA between CIC and niche cells[93-95]. Thus, SC actively recruit and activate those cells that in a feedback support their survival.

CSC also shape a niche for metastasizing tumor cells in selective organs in advance of tumor cell arrival, known as premetastatic niche. Tumor-derived growth factors stimulate resident fibroblasts to secrete fibronectin, which promotes attachment of hematopoietic progenitors expressing VEGF receptor (R)1 and α4. In addition, stromal fibroblasts-derived CXCL12 attracts CXCR4 expressing hematopoietic progenitors and CSC[96]. Meanwhile it is well established that TEX are the central actors in establishing a premetastatic niche in epithelial cancer[97-99] including PaCa[100,101].

Taken together, CSC maintenance depends on a crosstalk with the surrounding matrix and nearby as well as distant cells. There is strong evidence that TEX are the major player in this crosstalks.

Exosomes

Exosomes are small 40-100 nm vesicles. They are delivered by many cells and abundantly by tumor cells[102]. Exosomes biogenesis is initiated by the formation of early endosomes that become integrated as intraluminal vesicles (ILV) into multivesicular bodies (MVB). MVB can fuse with lysosomes for protein degradation. Alternatively, MVB fuse with the plasma membrane and release their ILV, which are termed exosomes[103].

MVBs are assembled from early endosomes sorted from the trans-Golgi network or from internalized membranes, where the endosomal sorting complex required for transport (ESCRT) plays an important role in vesicle traffic and loading. The ESCRT complex is composed of the subcomplexes ESCRT Ⅰ, Ⅱ and Ⅲ[104]. *Tsg* (tumor susceptibility gene)101 in the ESCRT complex Ⅰ binds ubiquitinated proteins and recruits ESCRT Ⅱ. ESCRT Ⅱ or Alix (ALG-2-interacting protein X) recruits ESCRT Ⅲ. ESCRT Ⅲ recruits a deubiquitinating enzyme that removes the ubiquitin tag from the cargo proteins prior to sorting into MVB[105]. Finally, the ATPase vacuolar protein sorting 4 (Vsp4) dissociates the ESCRT Ⅲ complex from the membrane. Additional essential partners in ESCRT-dependent exosome biogenesis are syndecans and transmembrane heparan sulfates, which interact with syntenin. Syntenin cooperates with CD63 and Alix[106]. Alternatively, cell membrane integrated tetraspanins and other proteins residing in glycolipid-enriched microdomains (GEM)[107] become incorporated into MVB, which is a sequel of the physical properties of GEM being prone for internalization[108]. Indeed, tetraspanins are essential for exosome generation as demonstrated by defective exosome secretion in CD9 knockout mice[109]. A third pathway proceeds *via* proteolipids (PLP). In cholesterol and ceramide-rich compartments, the PLP colocalize with flotilin and glycosylphosphatidylinositol. Exosome biogenesis *via* PLP depends on ceramide production by neutral sphinomyelinase-2. Sphingosine-1-phosphatase and diaglycerol (DAG) are engaged in cargo sorting[110].

Early endosomes hike through the cytoplasm in advance of being released as exosomes. Rab proteins, a subfamily of small GTPases, associate *via* geranylgeranyl modifications with membranes, regulate vesicle budding, tethering and fusion. Rab4 and rab5 mostly are recovered on early endosomes, rab11 is engaged in juxtanuclear recycling endosome traffic, rab7 and rab9 are recovered in late endosome and MVB. Rab35 and rab11 are engaged in endocytic recycling. Rab proteins regulate vesicle traffic *via* the interaction with actin and microtubules. Rab11 recruits myosin and dynein, moving of late endosomes along microtubules being dynein-dependent. Docking on the plasma membrane *via* kinesin is regulated by rab25. Rab GTPase activating proteins (GAP) and Rab27b are engaged in exosome release, where SNARE proteins (soluble-N-ethylmaleimide-sensitive fusion protein-attachment protein receptors) (v-SNARE) pair with

SNARE-binding partners (t-SNARE) on vesicles[111]. Finally, during the invagination of early endosomes into MVB, the exosome cytoplasm receives its cargo (Figure 1A).

Exosomes are composed of a lipid bilayer containing transmembrane proteins. The small plasma contains proteins, mRNA, non-coding RNA and DNA. The potential cargo is estimated to approximately 100 proteins and 10000 nucleotides[102]. The origin of the early endosomes determines the membrane lipid and protein composition of exosomes. Loading of the small plasma is a non-random, selective process that is not yet fully clarified.

As reviewed[112], exosomes contain phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, prostaglandins, and lysobisphosphatidic acid and are enriched in sphingomyelin, cholesterol, GM3, and phosphatidylserine[113]. Phosphatidic acid, diglycerides, and ceramides, lipid second messengers are involved in exosome biogenesis, where proteins of the ESCRT machinery interact with various lipids or lipid-related enzymes. Vps4 interacts with an oxysterol binding protein[114] making a link with cholesterol metabolism. In fact, lipids in general, and more specifically sterols and fatty acids play a key role in Golgi/endosome/vacuole sorting[115]. Furthermore, the high content of sphingomyelin, cholesterol and GM3 increase overall rigidity and stability[116,117]. Phosphatidylserine facilitates exosome fusion and fission[118] and lysobisphosphatidic acid is involved in intracellular fusion and budding[119]. Packaging of miRNA into exosomes requires the neutral sphingomyelinase2[120].

Exosomes contain approximately 7000 proteins[121,122]. Constitutive exosomal proteins are structural vesicle components and proteins involved in vesicle biogenesis and trafficking. For GEM-derived exosomes, including tetraspanin networks, higher order oligomerization is important[123]. There is strong evidence that exosomes derived from tetraspanin-enriched microdomains contain the unchanged membrane complex including attached cytoplasmic components[124], which may account for GEM-derived exosomes in general. In raft-derived exosomes ceramide forming sphingolipids play an important role in exosome loading[125]. Otherwise, mono-ubiquitination, acylation or myristoylation are known to facilitate sorting of proteins into exosomes[126,127].

Tetraspanins are the most abundant exosome component[107]. They are enriched 7-124 fold in exosomes compared to the parental cells[128]. Additional abundantly recovered exosome components are adhesion molecules, proteases, MHC molecules, heat shock proteins (HSP), TSG101, Alix, annexins, cytoskeleton proteins (actins, cofilin-1, ezrin/radixin/moesin, profilin-1, tubulins), metabolic enzymes, cytosolic signal transduction molecules and ribosomal proteins. Some of these constitutive exosomal proteins are recruited *via* their association with proteins engaged in exosome biogenesis, which is well explored for tetraspanin-associated integrins and proteases[129,130], HSP-associated transferrin receptor and cytosolic proteins associated with transmembrane proteins or attached to the inner membrane of invagination prone GEM[131]. Cell type-specific exosomal proteins are most comprehensively explored for cancer/CSC-TEX. Melanoma TEX contain MART1, epithelial cancer cell-derived TEX contain EpCAM and gastrointestinal cancer derived TEX contain cld7, glioblastoma TEX contain EGFRVIII and TEX of docetaxel-resistant prostate cancer cells contain multidrug resistance gene 1[132-134]. TEX also contain c-Met, mutant KRAS and tissue factor[132,135,136]. Notably, all CSC markers are recovered in TEX[137,138].

Exosomes also contain mRNA, rRNA, tRNA, miRNA, lncRNA, mitochondrial DNA and short DNA sequences of retrotransposons[139-141], protected from degradation by the double lipid membrane[142,143]. RNA and DNA sorting into exosomes required further elaboration. Annexin-2 recruits specific RNAs by binding [144]. A zip code in the 3′-UTR guides miRNA recruitment. It is facilitated by coupling of the RNA-induced silencing complex (RISC) to sorting complex components. GW182 containing GW bodies promote continuous assembly/disassembly of membrane-associated miRNA-loaded RISC. Finally, a specific EXO motif (GGAG) controls miRNA loading by binding to the heterogeneous ribonucleoprotein A2B1 (hnRNPA2B1), where sumoylated hnRNPA2B1 binds to an RNA transport signal (RTS or A2RE) in the 3′ UTR containing the EXOmotifs[145]. The mechanisms for selective recruitment of lncRNA into exosomes remains to be explored[146].

Though next-generation sequencing can be expected to shortly unravel exosomal DNA, coding and noncoding RNA[147], microarray analysis already provided some valuable information, particularly on exosomal miRNA. MiRNA constitutes only 1%-3% of the human genome, but due to multiple targets, miRNA control about 30% of the coding genes. With perfect base pairing, mRNA is cleaved by Argonaut (AGO), upon imperfect binding, translation is repressed[148]. Knowledge on miRNA greatly fostered progress in oncology. Selected miRNA could be linked to prognosis, disease progression, recurrence and metastasis[149]. miRNA plays an important role in EMT[150], maintenance of CSC[151], tumor invasion, migration and angiogenesis[152]. Most studies being not specifically concerned about TEX CSC miRNA, two publications should be mentioned that described selective TEX miRNA recovery in a subtype of $CD44^+$ breast cancer cells[153] as well as a report on $CD133^+$ melanoma TEX that revealed 49 miRNA not detected in TEX from the parental cells, 20 of these selectively recruited miRNA displaying cancer related function[154]. lncRNA makes up approximately 3% of the exosomal RNA. It also is transferred into host cells. Deep sequencing results are awaited for a profound evaluation on clinical relevance[155] (Figure 1B).

Taken together, CSC/metastasizing tumor cells

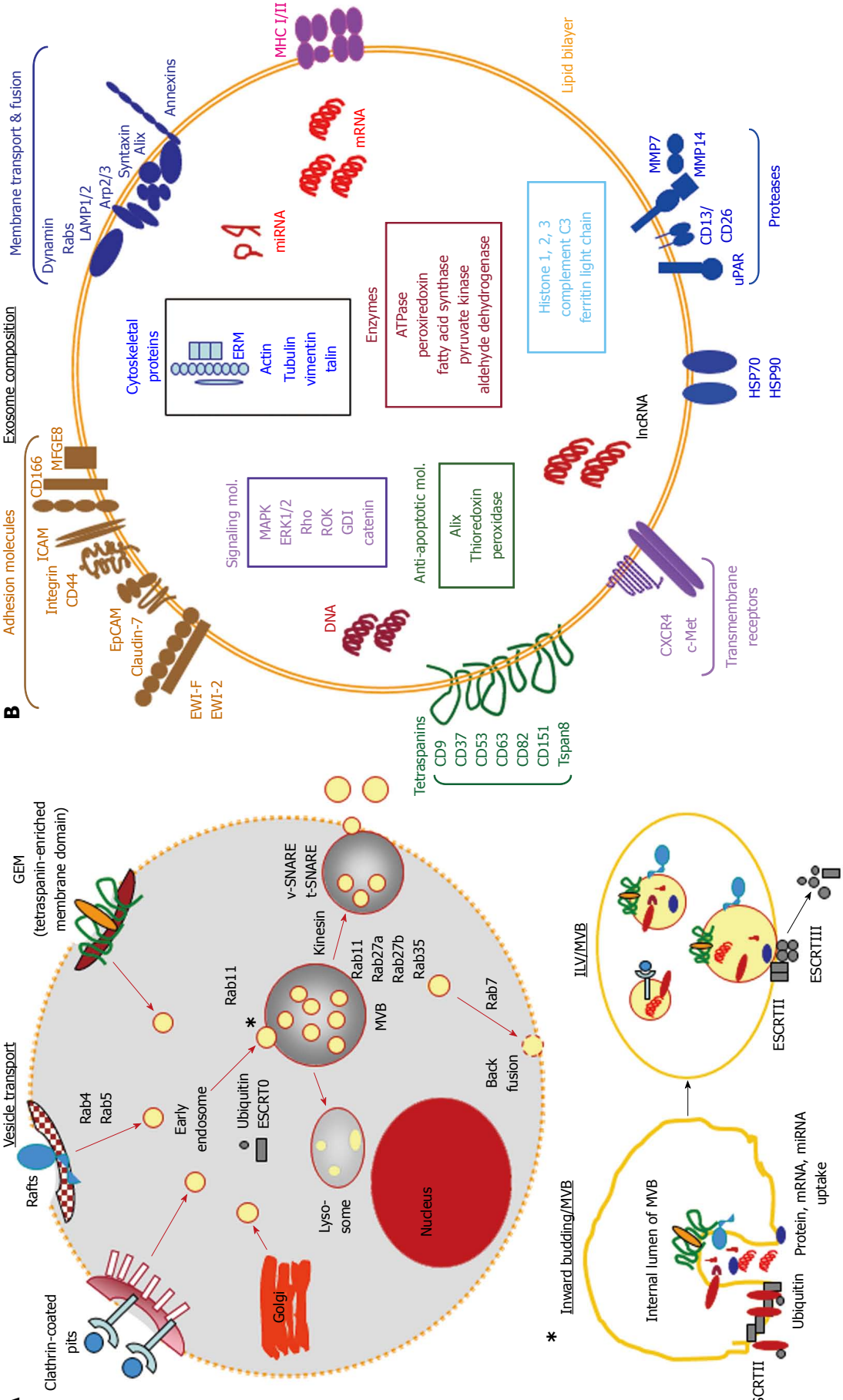

Figure 1 Exosome biogenesis and release. A: Exosome biogenesis is initiated by the generation of early endosomes delivered by the Golgi complex or by invagination of defined membrane microdomains such as clathrin coated pits, rafts and glycolipid enriched membrane microdomains, which are by scission separated from the originating membrane. Early endosomes are budding into multivesicular bodies During this process the small cytoplasm of endosomes is loaded with proteins, mRNA and DNA. The invaginated early endosomes dissociate from the membrane of multivesicular bodies and are then called intraluminal vesicles. Early endosomes and multivesicular bodies are guided along microtubuli by transporter proteins and transporter complexes, where monoubiquitination, different Rabs, ESCRT complexes and SNARE proteins account for distinct guiding routes; B: Exosomes are characterized by a lipid bilayer enriched in cholesterol, sphingomyelin, GM3 and phosphatidylserine and membrane proteins that vary with the donor cell and the originating membrane microdomain, tetraspanins being a constitutive and highly enriched component. Signal transduction and cytoskeletal proteins are mostly recruited *via* the association with the inner plasma membrane. Cytosolic proteins, coding and noncoding RNA and DNA are selectively recruited. Of note, to our knowledge, all CSC markers are recovered and enriched in exosomes. CSC: Cancer stem cells; GEM: Glycolipid-enriched microdomains; ESCRT: Endosomal sorting complex required for transport; MVB: Multivesicular bodies; ILV: Intraluminal vesicles.

display SC features, which becomes most prominent during EMT and the establishment of and crosstalk with CSC niches including the premetastatic niche, supposed to be promoted by TEX. Thus, the question arose on the specific equipment of CSC that provides the base of these activities. Besides their functional characterization, CSC are defined by protein marker panels, which are frequently used for CSC/CSC-TEX isolation[119-122]. Functional importance of these CSC markers only recently received attention. We hypothesize that CSC markers are the major players including the assembly of CSC-TEX.

PANCREATIC CANCER STEM CELLS MARKERS

Prominent Pa-CSC markers are CD44v6, c-Met, Tspan8, α6β4, CXCR4, EpCAM and prominin-1 (CD133)[35,156-162], most of which are also recovered in other gastrointestinal CSC. Importantly, these markers were demonstrated to be of functional relevance and to cooperate.

CD44v6 and c-MET

CD44v6 is a CSC marker in PaCa and colorectal adenocarcinoma (CoCa)[35,162-166]. Its functional engagement was repeatedly demonstrated by the impact of CD44v6 overexpression and targeted deletion on metastasis formation[100,167-169].

CD44v6 is a splice variant of CD44, an abundantly expressed adhesion molecule and the prime receptor for hyaluronan (HA)[170], the globular N-terminal region also binds collagen, laminin, fibronectin (FN) and selectins[171-173]. CD44v6 contains additional binding sites for the chemokine osteopontin (OPN)[174,175], HGF and VEGF[176,177] (Figure 2A). *Via* chemokine binding , CD44v6 becomes engaged in motility. OPN is chemotactic and haptotactic and as such important for cell recruitment[178] and motility. Thus, $p53^{ko}CD44^{ko}$ mice develop primary tumors at a comparable rate to $p53^{ko}$ mice, but $p53^{ko}CD44^{ko}$ tumors do not metastasize[165,179]. CD44v6 has binding sites for cytokines. *Via* bound cytokines, CD44v6 takes over a coordinating role in RTK activation[180,181], which is detailed below for the cooperation with c-Met. The cytoplasmic tail of CD44 plays an important role in signal transduction. It contains binding sites for the cytoskeletal proteins ezrin, radixin, moesin (ERM) and ankyrin. Ankyrin mediates contact with spectrin and is involved in adhesion and motility[182]. ERM proteins are engaged in regulating migration, cell shape and protein resorting in the plasma membrane[183]. The N-terminus of activated ERM proteins binds to CD44 and the C-terminus binds to F-actin, linking CD44 to the actin cytoskeleton[184]. The binding of CD44 to cytoskeletal linker proteins influences signaling pathways downstream of CD44, which expands the range of CD44-mediated functions. Finally, CD44 can be cleaved by ADAMs and MMP-14[185]. After ectodomain cleavage, CD44 becomes accessible to the presenilin/γ-secretase complex, which triggers intramembrane CD44 cleavage, setting free the CD44 intracellular domain (CD44-ICD). CD44-ICD acts as a co-transcription factor that potentiates beside others CD44, MMP9, MMP3 and HIF2α transcription[186-188]. The last point to mention is of central importance for the functional activity of CD44v6 as a CSC marker. CD44v6 O-glycosylation, the transmembrane region and the cytoplasmic tail affect the membrane subdomain localization, where recruitment into GEM[189] promotes the interaction of CD44 with extracellular ligands and the association with other transmembrane and cytoplasmic molecules[190]. These associations are most crucial for the activity of CD44 in signal transduction, migration, apoptosis resistance, premetastatic niche preparation[191,192] and the cooperation with additional Pa-CSC markers[98], one example being the recruitment of CXCR4 into GEM upon ligand binding, where it associates with CD44[193,194].

Another CD44 feature of special importance for CSC migration is the cooperativity with proteases. CD44 concentrates MMPs at the cell surface and CD44 aggregation *via* HA binding further facilitates MMP binding[187]. By the interaction with HA the production of uPAR, MMP2 and MMP9 is stimulated[195]. Furthermore, the CD44-ICD binds to a MMP9 promoter response element actively supporting MMP9 transcription[187]. ProMMP2 and proMMP9 become activated through CD44v-associated MMP14. Cell-bound MMPs being protected from their inhibitors, this allows for ECM degradation forming space for invading tumor cells[196]. In addition, TGFβ activation through CD44-associated MMP9, promotes angiogenesis and invasion and several mechanisms of TGFβ-promoted apoptosis become silenced[197,198] (Figure 2B-G).

Finally, as recently reviewed, CD44/CD44v6 and CD44/CD44v regulates miRNA engaged in metastasis[180,199]. First to note, the CD44 3'-UTR binds several miRNA (miR-328, miR-491, miR-671, miR-512-3p) such that collagen 1 and FN are released from repression[200]. Furthermore, upon activation Oct4-Sox2-Nanog are recruited to CD44v3 and translocate into the nucleus, where they initiate miR-302 transcription, which suppresses epigenetic regulators and increases expression of cIAP-1, cIAP-2 and XIAP strengthening drug resistance[201]. We described abundant recovery of miR-494 and miR-542-3p in TEX from a $CD44v6^+$ rat PaCa that promoted cadherin-17 downregulation accompanied by MMP release from repression[202]. These sporadic findings will become consolidated by deep sequencing. Nonetheless, they provide first support for the engagement of CD44/CD44v6 in CSC activities also *via* miRNA.

Another Pa-CSC marker is the RTK c-Met[156,203], which contribution relies at least in part on its cooperativity with CD44v6. c-Met becomes activated by binding its ligand HGF. As CD44v6 bind HGF, c-Met

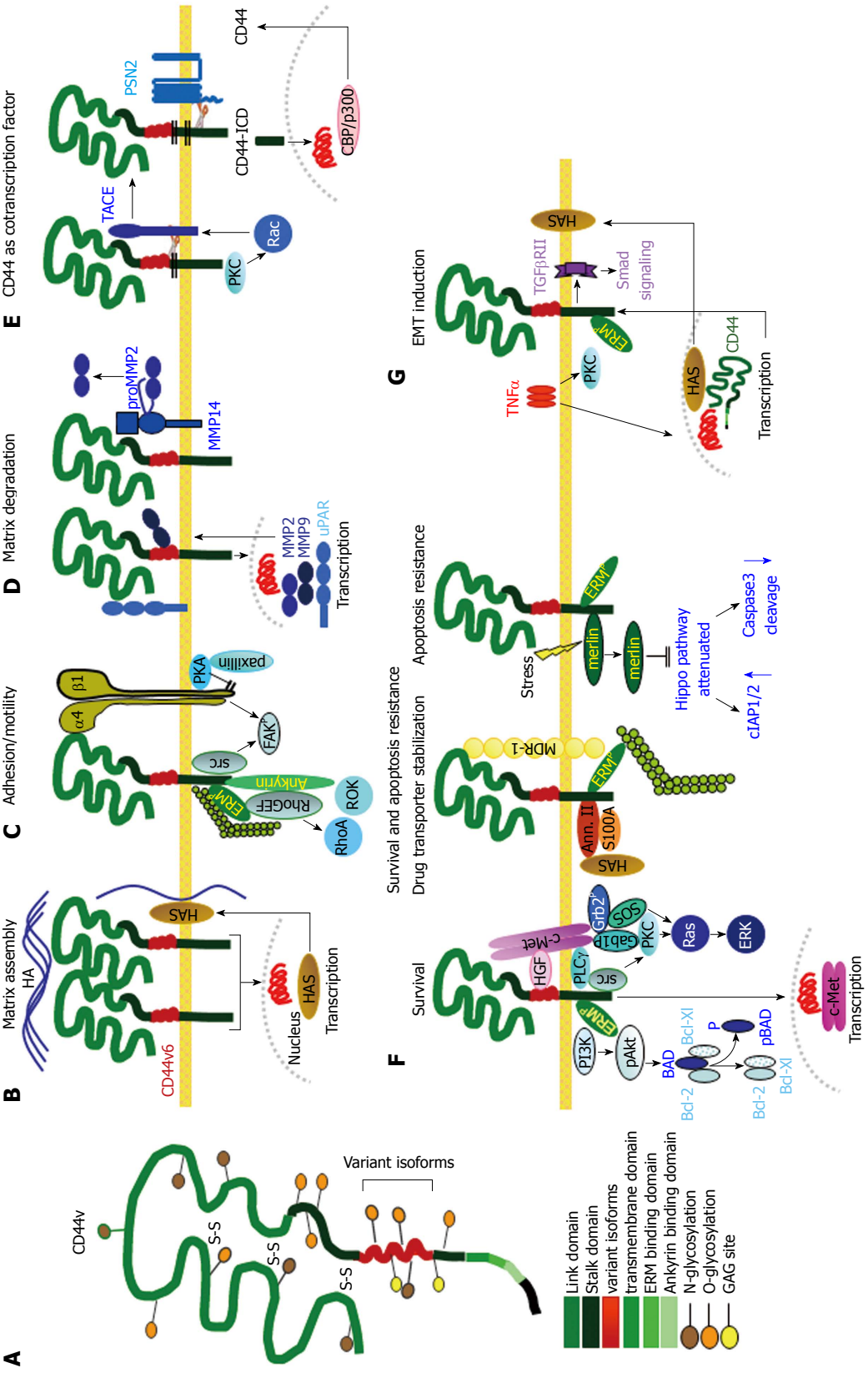

Figure 2 Cancer stem cells supporting activities of CD44v6. A: Structure of CD44 including insertion of variant exon products; B: CD44v6 is engaged in assembling the HA matrix by inducing HAS transcription. The matrix supports CD44 activation; C: GEM-located CD44/CD44v6 is src associated and cooperates with adjacent integrins. Activated ERM proteins and Ankyrin link CD44 to the cytoskeleton and initiate RhoA and ROK activation, which together play an important role in CSC motility; D: CD44v6 is engaged in uPAR and MMP transcription. It associates with MMP14, which captures MMP2 and MMP9, supporting ECM degradation and remodeling; E: GEM-located CD44v6 can be cleaved by TACE and subsequently by PSN2. CD44-ICD is a powerful cotranscription factor, which induces beside others CD44 transcription; F: There are several pathways, whereby CD44v6 supports CSC survival and apoptosis resistance. It cooperates with c-Met, which is brought into vicinity by CD44v6-bound HGF; a complex of CD44, Annexin II, S100A and HAS stabilizes MDR1; stress induces merlin phosphorylation, which dissociates from CD44 and hampers activation of the Hippo pathway; G: One pathway of CD44-linked induction of EMT relies on TNFα that fosters CD44 expression and CD44 cooperativity with TGFβRII promoting Smad signaling. CD44 also is engaged in activation of Nanog and in repressing miRNA transcription that targets EMT proteins (not shown). The majority of these CSC supporting activities of CD44/CD44v6 rely on GEM-recruited CD44. CSC: Cancer stem cells; GEM: Glycolipid-enriched microdomains; ERM: Cytoskeletal proteins ezrin, radixin, moesin; EMT: Epithelial mesenchymal transition; TNFα: Tumor necrosis factor α; TGFβ: Transforming growth factor β; TACE: TNFα converting enzyme.

comes into proximity of CD44v6, which contributes to c-Met activation. c-Met is a transmembrane heterodimer[204]. Upon ligand binding the intracellular tyrosine kinase domain becomes activated through tyrosine phosphorylation in the carboxyterminal end providing docking sites for adaptor and intracellular kinases[205]. The major adaptor protein is Grb2, prominent downstream signaling cascades are MAPK, PI3K/Akt and *via* these two pathways src, STAT3, nuclear factor κB (NFκB), FAK and β-catenin[206]. CD44v6-initiated c-Met phosphorylation requires the cytoplasmic tail of CD44 and the interaction with ERM proteins for activation of the Ras-MAPK pathway[204], the PI3K-Akt pathway and Wnt/β-catenin signaling[207,208]. In addition, CD44v6 regulates c-Met transcription[100,209]. Similar observations account for the cooperation of CD44v6 with insulin-like growth factor-1- and PDGFR[209,210]. Major cellular responses of c-Met activation include migration, invasion, stemness maintenance, apoptosis resistance and EMT. c-Met can directly interact with E-cadherin, which drives nuclear accumulation of β-catenin and leads to disruption of cell-cell adhesion[211,212].

Tspan8 and α6β4

Tetraspanins are a family of small proteins passing the membrane 4 times[213]. Two family members, CD151 and Tspan8 are associated with tumor progression[107,214,215]. For Tspan8 this accounts particularly for gastrointestinal cancer[216-226], where we provided evidence that Tspan8 is enriched in Pa-CSC[35,130,162]. What qualifies Tspan8 as a functionally relevant CSC marker?

Tetraspanin cross the membrane 4 times with the short N- and C-terminal tails being located in the cytoplasm. Tetraspanins have a small extracellular loop between transmembrane region 1 and 2 and a large extracellular loop between transmembrane regions 3 and 4. The large extracellular loop contains highly conserved cyteines that provide the essential signature of tetraspanins differentiating them from other 4-span molecules. The large extracellular loop accounts for dimerization and for interactions with non-tetraspanin partner molecules. Polar residues in the transmembrane regions stabilize the tertiary structures[227-230]. Palmitoylation is required for initiating tetraspanin-tetraspanin web formation, protects from degradation and provides a link to cholesterol and gangliosides, which supports the formation of GEM[231-236]. Some tetraspanins avail on a tyrosine-based sorting motif that promotes internalization. Yet, internalization can also proceed *via* associated molecules with a sorting motif[237-239] (Figure 3A).

With few exceptions, tetraspanins have no direct ligands. Instead, they form complexes by interacting between themselves and a large variety of transmembrane and cytosolic proteins[240]. The most prominent tetraspanin partners are integrins[241,242], for Tspan8 particularly α3β1, α6β1 and α6β4[243-245], but α4β1 and α5β1 also associate with Tspan8[246,247]. Proteases are an additional class of functionally important tetraspanin partners[248], Tspan8 associating with the dipeptidase CD26, MMP14, TACE (ADAM17), MMP2 and 9[130,226,245,246,249]. Tetraspanins associate with growth factor receptors[250,251], G protein coupled receptors (GPCR) and their intracellular associated heterotrimeric G-proteins[252] as demonstrated for the relaxin receptor in prostate cancer[253] Prominent cytosolic signal transduction molecules co-immunoprecipitating with tetraspanins are protein kinase C (PKC), a type Ⅱ phosphatidylinositol 4 kinase (PI4KII) and phospholipase Cγ (PLCγ)[254-256], these associations being also relevant for Tspan8[243,257]. Most important for the activity of Tspan8 as Pa-CSC marker are the associations with α6β4, CD44v6 and EpCAM[243-245,258,259].

Besides providing a signaling platform, tetraspanin complex location in GEM facilitate vesicular fusion and/or fission[107,260-262], which is supported by a tyrosine-based sorting motif of tetraspanins or associated proteins[263].

Taking into account the reversibility of palmitoylation and the instability of membrane microdomains, it can be expected that tetraspanin activities vary considerably depending on the activation state of the cell. The fact that tetraspanins act *via* laterally associated molecules and only exceptionally *via* ligand binding, promotes their large array of functions. Nonetheless, there is a common theme. Tetraspanins promote adhesion, spreading, motility, cable formation, invasion, membrane microdomain internalization and vesicle formation. These activities rely on integrin compartmentalization, internalization, modulation of integrin signaling and integrin biosynthesis[241,242,264]. Invasiveness depends on the association with proteases or could proceed through modulating MMP transcription and secretion[245,248]. The involvement of tetraspanins in fusion events has been convincingly demonstrated by the failure of egg-sperm fusion in CD9 and CD81 knockout mice[265], the involvement in cell-virus and cell-parasite interactions[266,267] and their morphogenic features[268,269].

Tspan8 shares most of these activities with other tetraspanins[107]. In gastric cancer Tspan8 promotes metastasis *via* activation of the MAPK pathway[223]. It contributes in particular *via* its strong association with α6β4, which is only seen upon α6β4 activation by ligand binding. The Tspan8-α6β4 association strikingly increases tumor cell motility and is accompanied by ezrin, paxillin, src, FAK, and rac/ras activation[245]. Dysregulated adhesion and motility also account for colorectal cancer metastasis[216]. Invasion is supported by the association with TACE, MMP2 and MMP9 and a weak association with MMP14, which could be indirect *via* the association with CD44v6[245]. In esophageal cancer, too, cooperativity between

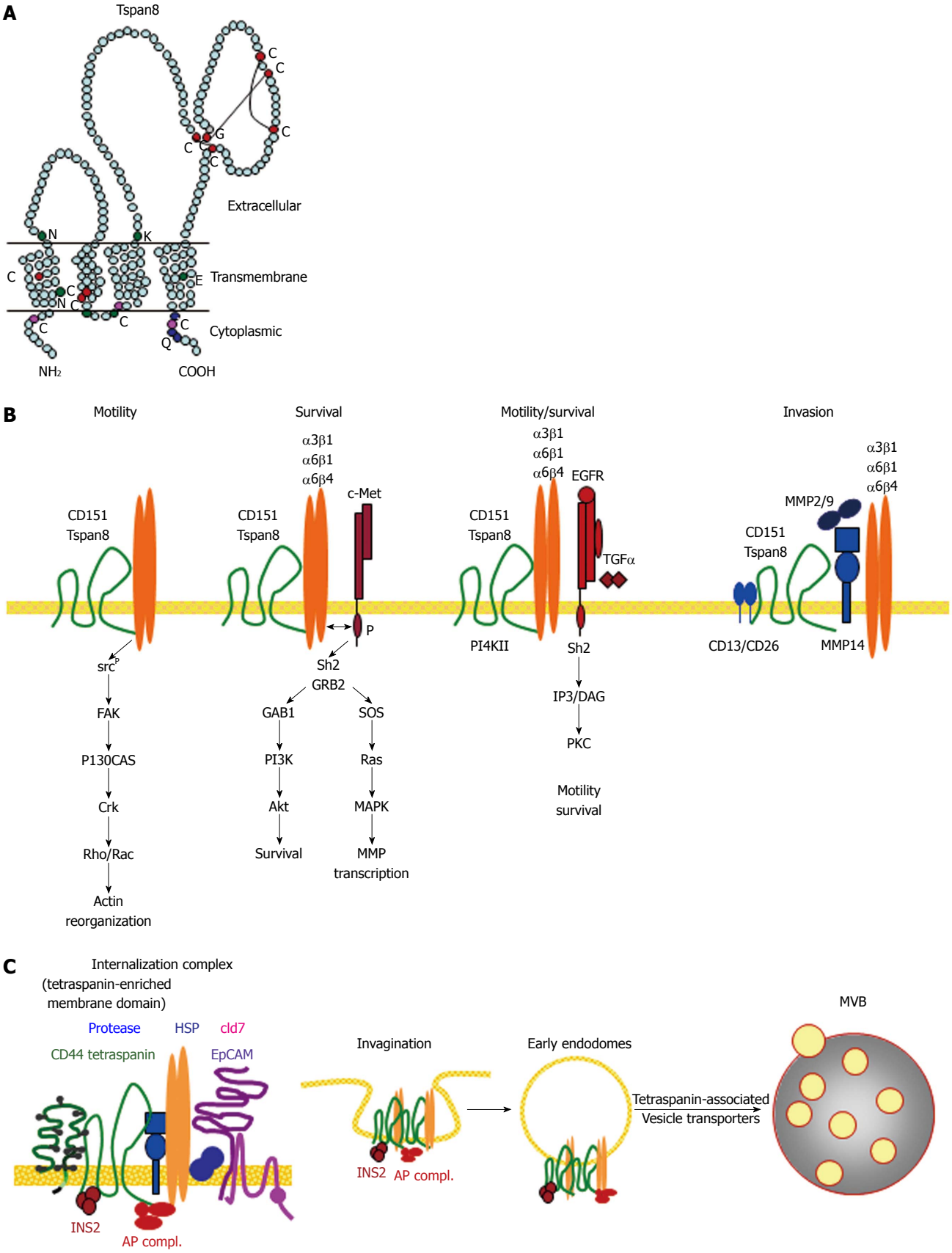

Figure 3 Cancer stem cells supporting activities of Tspan8. A: The structure of Tspan8 showing the prominent large extracellular loop, which is the main binding site for laterally associated molecules; B: Dominant partners of Tspan8 and CD151 are integrins and proteases. Tspan8 and CD151 also associate with RTK, CD44v6 and EpCAM. The integrin associations promote CSC motility, the RTK associations survival and the protease associations invasiveness: C: the strongest contribution of Tspan8 in support of CSC relies on its engagement in GEM complex located molecule internalization. Tspan8 is also involved in vesicle traffic. The importance of Tspan8 in CSC is linked to recruiting additional CSC markers into GEM and in contributing to the transfer of the GEM complex into TEX. CSC: Cancer stem cells; GEM: Glycolipid-enriched microdomains; MVB: Multivesicular bodies; PKC: Phophokinase C; RTK: Receptor tyrosine kinase.

Tspan8 and ADAM12m promotes metastases[226]. We consider the engagement in EMT gene transcription *via* its association with β-catenin[130] and Notch[270], also described for CD44[271] and EpCAM/cld7-associated EpCAM[272,273] and the cooperativity with CD44v6, α6β4 and the EpCAM-cld7 complex[98,266] as most important for the contribution of Tspan8 to the CSC phenotype of PaCa (Figure 3B). The contribution of Tspan8 to exosome generation (Figure 3C) and, as outlined below to targeting[107], adds to the central importance of Tspan8 in Pa-CSC.

As mentioned, one of the Tspan8 partners is the α6β4 integrin, the linkage between α6β4 and the tetraspanins CD151 and Tspan8 being repeatedly reported[264,274,275] and ample evidence is provided for the engagement of α6β4 in PaCa progression[130,243,276-280].

The α6β4 integrin is unique in structure and subcellular localization. Distinct to other β chains, the cytoplasmic domain of β4 is over 1000 amino acids long. Towards the C terminus it contains two pairs of type Ⅲ fibronectin-like modules, which contain tyrosine phosphorylation and proteolytic cleavage sites. Furthermore in the resting state α6β4 is located in hemidesmosomes anchoring epithelial cells *via* laminin binding to the basement membrane, indicating its interaction with keratin filaments opposing the actin filament association of other integrin β chains[281]. However, upon stimulation, *e.g.,* by wounding, stress and in tumor cells, hemidesmosomes become disassembled and α6β4 is driven into GEM, preferentially in F-actin protrusions[207,264,282-284]. Palmitoylation of the β4 chain support the GEM localization and β4 initiated signal transduction[285,286]. Upon disassembly of hemidesmosomes, the β4 cytoplasmic domain becomes phosphorylated preferentially *via* PKCα[287,288]. Phosphorylated α6β4 binding to laminin activates both PI3K and ras homolog family member A (RhoA) small GTPases[280,289,290]. Alternatively to laminin binding, α6β4 activation can be initiated by cooperation with growth factor receptors including ErbB-1,2,3 and c-Met[207,290-296], which promotes activation of PI3K, Akt, MAPK, and Rho small GTPases pathways[207,289,297-299].

α6β4 affects cell survival and angiogenesis[244,289,297,300,301] and was reported to alter expression of > 500 genes[302]. Its dominating activity relies in promoting tumor cell invasiveness[130,274,278,279,290], which fits well to its association with tetraspanins in GEM. Notably, there is evidence for engagement in stemness[35,130,162,303-306]. In PaCa it is predominantly associated with Tspan8 and expression is upregulated in Pa-CSC[35,162]. The impact of this association may gain further weight by the joint recovery in PaCa TEX[130,204].

CXCR4

CXCR4 is a G protein-coupled chemokine receptor[307], upregulated in CSC, particularly migrating CSC[308] including metastatic PaCa and lung cancer cells with CSC-like properties, which show upregulated CXCR4 and CD133 expression[309,310]. CXCR4 is suggested to contribute to tumor growth, angiogenesis, therapy resistance[90,311-313] and to have a strong impact on metastasis including the recruitment to specific sites such as the bone marrow[314]. In 85% of PaCa CXCR4 expression is increased and was identified as an independent factor for poor prognosis[162,315,316].

After stromal-derived factor (SDF)1 binding CXCR4 and possibly extracellular HSP90 colocalize to lipid rafts, which facilitate together with HSP90 signal transduction[317]. Activated CXCR4 increases intracellular calcium levels and induces a phosphorylation cascade, which is terminated by CXCR4 internalization[318]. After chemokine binding the heterotrimeric G protein is activated and dissociates in GTP-bound α and βγ subunits. Cell motility is regulated by several phosphorylation cascades, which include src and Akt as the central node. Akt phosphorylates several downstream targets that reorganize actin fibers. The βγ subunit activates PLCβ and PI3K. PLCβ cleaves PIP2 in IP3 and DAG, where IP3 induces the release of Ca from intracellular stores. DAG together with Ca activates PKC and MAPK. PI3K activation leads to activation of focal adhesion components and cytoskeletal proteins contributing to reorganization of the actin cytoskeleton. Actin polymerization is stabilized by HSP90, which promotes the formation of filipodia and directed cell migration[319]. Activated PI3K additionally activates *via* Akt the mitochondrial antiapoptotic signaling pathway[320]. Activated Akt also contributes to β-catenin stabilization and gene transcription[321]. Signaling through Gαi is linked to transcription through PI3K/Akt, NFκB, mitogen-activated protein kinase kinase 1/2 and leads to activation of the Ras and Rac/Rho pathways[322]. Ligand binding induced dimerization results in G-protein-independent signaling with activation of the JAK/Stat pathway[323], which might be accompanied by polarization[324]. Finally, CD44 binding to human epidermal growth factor receptor 2 (HER2) supports CXCR4 expression in gastric cancer by suppressing transcription of miR-139, which targets CXCR4[325].

There are several reports on the association of CXCR4 with tetraspanins in hematological malignancies[326,327], where the GEM located complex cointernalizes and is recovered in TEX[328]. We recovered CXCR4 and Tspan8 in PaCa TEX[35,130] and CXCR4 expressing TEX from a metastatic CoCa line promote metastasis formation of poorly metastatic lines. The authors speculate that this is due to recruiting $CXCR4^+$ stroma cells to create a metastasis-permissive environment[329].

In brief, CXCR4 increases the motility of metastasizing CSC. Recruitment into GEM facilitates cooperativity with addition GEM-located CSC markers as well as internalization and recovery in TEX (Figure 4).

EpCAM and claudin 7

EpCAM (EpC) is a prominent CSC-marker in colorectal, pancreatic, liver and breast cancer[330-332], but infor-

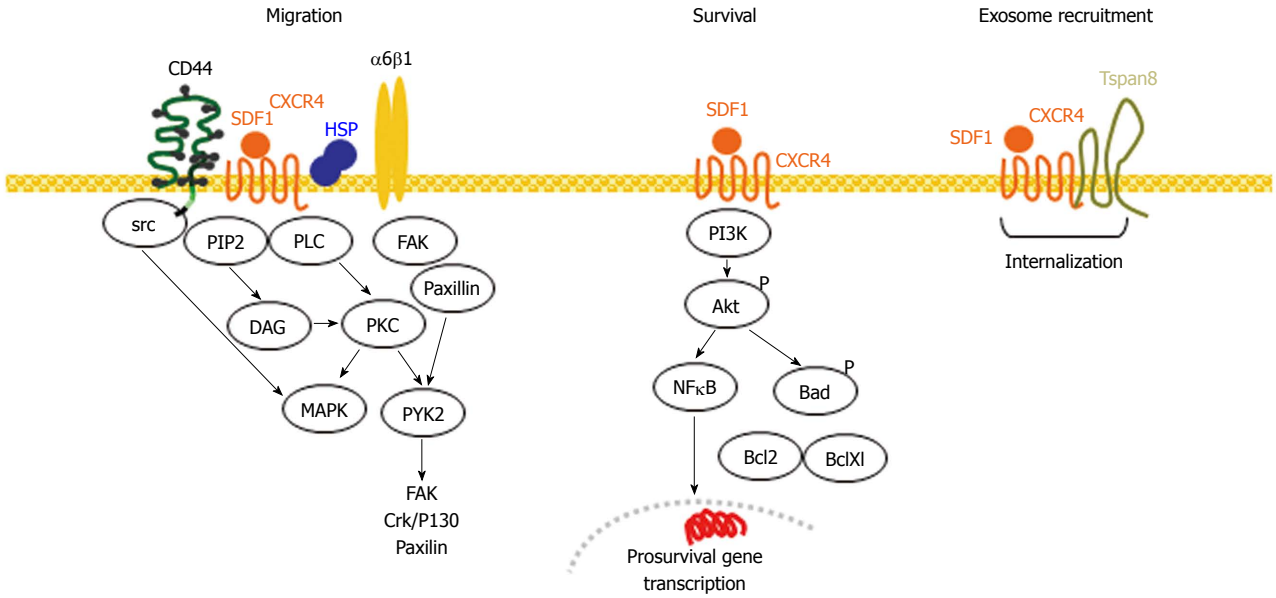

Figure 4 CXCR4, a marker of migrating cancer stem cells. CXCR4 becomes activated by SDF1 binding, which in concert with CD44, integrins and HSP initiates several signaling cascades that promote directed motility. CXCR4 also activates the PI3K/Akt pathway promoting antiapoptotic protein activation and prosurvival gene transcription. Activated CXCR4 becomes recruited into GEM, where in Pa-CSC the association with Tspan8 supports internalization. CXCR4 is recovered in TEX. In Pa-CSC CXCR4 cooperates with CD44(v6), laminin binding integrins and Tspan8 in TEM and is recruited into TEX. CSC: Cancer stem cells; GEM: Glycolipid-enriched microdomains; NFκB: Nuclear factor κB; TEX: Tumor exosomes; HSP: Heat shock protein; PLC: Phospholipase C; PKC: Phophokinase C; PI3K: Phosphatidylinositol-4,5-bophosphate 3 kinase; MAPK: Mitogen-activazed protein kinase; SDF1: Stroma-derived factor 1.

mation is limited, whether EpC fulfills CSC-related tasks[333-336]. In gastrointestinal cancer evidence was provided that CSC activity of EpCAM requires support by claudin 7 (cld7)[259,273,337-341].

EpC is a tetramer forming transmembrane molecules, which mediates homophilic cell-cell adhesion[342]. This weak homophilic binding is only seen in E-Cadherin cells due to EpC interfering with E-cadherin *via* disrupting the link between β-catenin and F-actin[343]. Due to a response element to the Wnt downstream effector Tcf4 it fosters Wnt signaling responses[52,344]. However, EpC can also act as a Wnt derepressor *via* sustaining Lrp6 (LDL receptor related protein 6) retention[345]. EpC also can control motility *via* down-regulation of PKC[346] and by regulating MMP7 expression[347,348]. These activities are promoted by the cytoplasmic tail of EpCAM (EpICD), which forms a complex with β-catenin, FHL2 (four-and-half-LIM-only) and Lef-1. The complex relocates to the nucleus, initiating, c-myc, cyclinA and E transcription[349]. The finding that EpC cross-linking triggers TACE (TNFα converting enzyme), which cuts the extracellular domain such that the membrane-anchored intracellular domain becomes accessible to PSN2 (presenilin 2 N-terminal fragment), which cleaves the intracellular peptide, EpICD, opened a new window towards the activity of EpC as a CSC marker[11]. EpICD also initiates transcription of additional reprogramming genes like Oct4 and Nanog, which is accompanied by EMT with upregulation of vimentin, Snail, Slug and downregulation of E-cadherin in a murine colon cancer and a human hepatoma line[350]. This study did not take into account the expression of cld7. However, hepatocyte progenitors express, besides EpC, cld7[351] and in CoCa and PaCa, EpC associates with cld7[235]. Under physiological conditions, too, the EpC-cld7 association is vital, an EpC^{ko} mouse dying within one week after birth due to intestine destruction, which relies on the missing association of EpC with cld7[352]. These findings pointed towards a concerted activity of EpC and cld7 in tumor progression, which was confirmed by a $cld7^{kd}$ and an EpC^{kd} in a metastasizing line. Both knockdowns sufficed to wave metastatic growth[341].

Claudins, four-pass transmembrane proteins, were first described as TJ components that are engaged in sealing, formation of ion channels and organization of paracellular small organic solute flux[353-355]. The importance of clds, including cld7, was repeatedly demonstrated by targeted deletion. A $cld7^{ko}$ is lethal within 10 d after birth due to intestine destruction[356]. The authors speculate that gut destruction is promoted by a missing association with integrins and upregulation of MMPs. An intestine-specific conditional $cld7^{ko}$ mouse revealed a specific enhancement of paracellular small organic solute flux across the TJ including a major bacterial product that initiates colonic inflammation[357].

However, claudins are also found outside of TJ[358-362]. Claudins are PKA, PKC and myosin light chain kinase targets[363-367]. Importantly, cld phosphorylation can prohibit integration into tight junctions with the consequence of loss of epithelial cell polarization[368-370]. Cld7 also has palmitoylation sites[36,356,371] and palmi-

toylated cld7 is excluded from TJ[371], but partitioned into GEM, where it is associated with monomeric EpCAM[273,341,372]. As already mentioned, GEM harbor palmitoylated proteins and act as a scaffold for signal transduction and reorganization of the cytoskeleton[373-376]. GEM-located, palmitoylated cld7 promotes tumor progression by supporting motility and invasion. This was confirmed in PaCa and CoCa for the EpC-cld7 complex, which promotes motility and invasion[259,341,372] as well as drug resistance that is initiated by downregulation of Pten[341]. There is additional evidence for a shift towards EMT gene expression[273], palmitoylated cld7 contributing to the generation of EpICD[371], facilitated by the GEM location of TACE and PSN2. Further supporting the cld7-EpC complex functioning as a CSC marker, triple negative breast cancer cells are cld7$^-$, but cld7-associated rab25 is expressed in breast-CSC[377-379]. Finally, outlined above, GEM are prone for internalization and recruitment into exosomes, which facilitate the metastatic process[380], where we experienced that cld7 actively contributes to the vesicle transport *via* associating with vesicle transporters. In CoCA and Pa-CSC the EpC-cld7 complex is recovered in TEX[273,361].

Taken together, cld7 and palmitoylated cld7 apparently account for distinct, non-overlapping activities such that dependent on the cellular context, the functional engagement in TJ or in GEM is dominating. Only GEM-located, palmitoylated cld7 displays CSC activity, where EpC contributes due to its association with GEM-located cld7. The main activity of this CSC marker complex builds on apoptosis resistance and EMT gene expression (Figure 5). A contribution of cld7 to TEX biogenesis might further strengthen the impact on CSC activity.

Prominin-1

Prominin-1 (CD133) is a CSC marker in several cancer entities[381-384], including PaCa[156,308,385-390]. CD133 is a pentaspan protein[391,392]. It is suggested to be associated with the Notch pathway, which is accompanied by slow cell cycling and increased drug resistance[393,394] as well as Hedgehog signaling with an increased capacity of anchorage independent growth[395]. CD133 is also engaged in Akt, JNK, mTOR, MAPK and IL-8/CXCL1 signaling cascades[396]. These findings are well in line with CD133 supporting maintenance of stemness and point towards a possible engagement in EMT gene transcription. Furthermore, it is well documented that CD133 interacts with cholesterol and is concentrated in different types of membrane protrusions with different types of cytoskeletal bases, *i.e.,* actin for microvilli and tubulin for cilia. These different membrane protrusions also appear to be released in at least two types of vesicles[396,397]. The smaller vesicles resembles exosomes containing all the constitutive exosomal proteins and the exosomal lipid profile. These exosomes, which also contain prometastatic proteins like CD44 and ADAMs, are taken up by tumor cells and bone marrow derived stroma cells, the transfer of CD133 being accompanied by increased invasiveness and metastatic potential[154]. Whether the second type of exosomes proceeds *via* the PLP pathway[110], which could be suggested by the interaction of CD133 with cholesterol, remains to be elaborated. Irrespective of their origin, CD133$^+$ TEX are recovered in CoCa and PaCa[35,159,361].

Taken together, CD133 is engaged in multiple signaling pathways linked to metastasis and EMT. CD133 also is another Pa-CSC marker that is constitutively located in internalization-prone membrane domains and is recovered in TEX.

In brief, the dominating features of the Pa-CSC markers are their connectivity, their engagement in multiple signaling pathways and their location in internalization prone membrane domains, which accounts for the enriched recovery in TEX. By these characteristics, Pa-CSC markers are prone to contribute to motility, invasiveness and EMT. *Via* their enrichment in TEX they appear destinated for the crosstalk with the host and non-CSC.

PANCREATIC CANCER STEM CELL MARKERS AND THE EPITHELIAL MESENCHYMAL TRANSITION

There are different modes, whereby Pa-CSC markers can contribute to EMT, markers can be engaged in the regulation of EMT gene transcription factors, EMT gene related miRNA processing or can be targets of miRNA. Last, not least, they can be engaged in the transfer of EMT transcription factors or miRNA into TEX, where TEX could become the actual transporter of EMT. So far information on these topics are rather limited. One hindrance being the transient nature of EMT, which becomes aggravated by the definition of CSC as a population of cells, enriched but not purified by a variety of distinct procedures. An additional hindrance relies on the evaluation of overall expression of CSC markers, which does not take into account that CSC markers are mostly recruited into GEM, where they can fulfill distinct or opposing functions compared to activities outside of GEM, like anchoring epithelial cells to the lamina basalis ($\alpha6\beta4$) or contributing to epithelial cell sealing (cld7). Nonetheless, there are reports describing regulation of CSC markers by EMT genes and vice versa.

Pancreatic cancer stem cell markers and EMT gene regulation

There are several reports on the engagement of CD44 in EMT gene regulation. In PaCa Snail-1 is a downstream target of CD44. Snail regulates MMP14 expression, which supports invasion[398]. Another

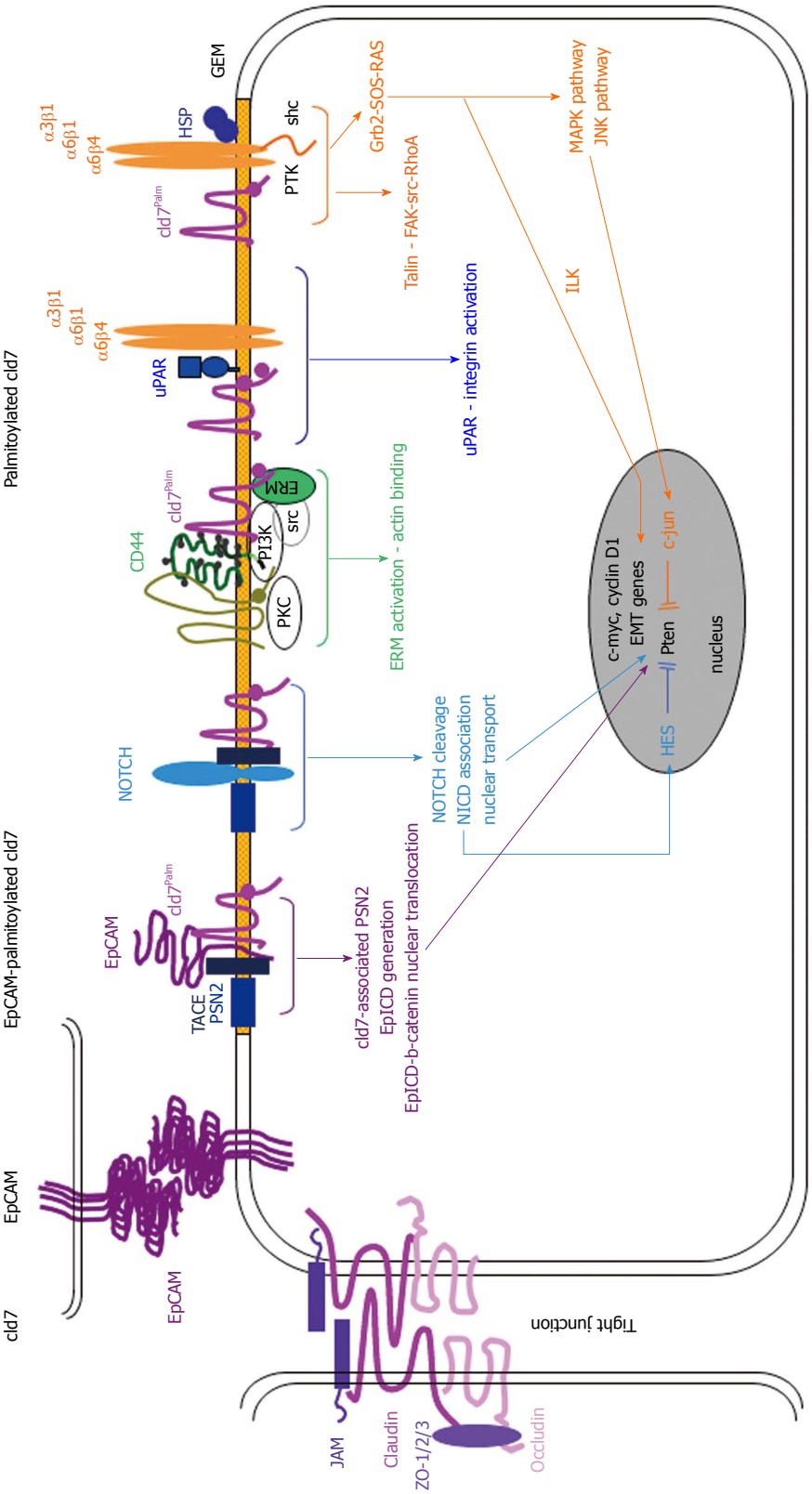

Figure 5 The EpCAM-palmitoylated claudin7 complex in pancreatic cancer stem cells. Upon palmitoylation the TJ protein cld7 becomes excluded from TJ and recruited into GEM, where it associates with monomeric EpC. Monomeric EpC becomes susceptible to GEM-located TACE and PSN2. EpICD associates with β-catenin and translocates to the nucleus acting as a cotranscription factor for c-myc, cyclinD1 and several EMT genes. The cld7-TACE-PSN2 complex also contributes to NOTCH cleavage. NICD contributes to HES activation, which inhibits Pten transcription. The palmitoylated cld7-uPAR association promotes integrin activation and transcription of EMT genes *via* ILK. Activation of the JNK pathway contributes to inhibition of Pten transcription. In Pa-CSC EpC becomes cleaved and involved in EMT gene transcription; palmitoylated cld7 additionally is engaged *via* Notch cleavage and integrin activation in apoptosis resistance. CSC: Cancer stem cells; GEM: Glycolipid-enriched microdomains; ILK: integrin-linked kinase; TJ: Tight junction; HSP: Heat shock protein; PKC: Phophokinase C; TACE: TNFα converting enzyme.

EMT transcription factor linked to CD44 is Zeb1. There is a self reinforcing feedback loop as Zeb1 and CD44 mutually sustain their expression. Notably, this study also describes an inverse linkage to CD44v expression, which is due to Zeb1 suppressing transcription of the epithelial splicing regulatory protein 1 (ESRP1)[399]. An excess of HA production also drives EMT, accompanied by upregulation of TGFβ and induction of Snail and Twist. Accordingly, inhibition of TGFβ-Snail signaling or Twist silencing abrogated the entrance into a stem cell state[400]. Furthermore, STAT3 is physically linked to CD44 and NFκB. This initiates the activation the catalytic subunit of telomerase (hTERT), which functions as a transcription cofactor in EMT[401]. Overexpression of Notch-1 induces CD44 and EpC expression and increases the formation of PaCa sphere formation, accompanied by the induction of the EMT markers Zeb1 and Hes-1[402]. In thyroid Ca, CD44-ICD binds to CREB, which promotes

cyclinD1 transcription[403] and in hepatocellular CA, a CD44/TM4SF5 (tetraspanin L six family member 5) association leads to activation of src, STAT3, Twist1 and Bmi1, supporting establishing the CSC phenotype and EMT[404]. In CoCa the CD44-HA ligation initiates src activation, which supports Snail activation that represses the stemness inhibitor miR-203[405]. Finally, GEM-located CD44 becomes internalized and migrates together with acetylated STAT3 to the nucleus. Nuclear CD44 binds to the promoters of several genes including c-myc and Twist1, promoting the EMT shift[406].

The tetraspanin TM4SF5 also is involved in EMT induction. TGFβ1-mediated Smad activation causes TM4SF5 expression, EMT and EGFR pathway activation. The finding that inhibition of EGFR activity abolished EMT suggests a link between Smad and the EGFR in TM4SF5 expression. In fact, inhibition of Smad or the epidermal growth factor receptor (EGFR) blocked TM4SF5 expression and EMT[407]. In human hepatocellular carcinoma cell lines TM4SF5 expression correlates with enhanced p27Kip1 (cyclin-dependent kinase inhibitor 1B) expression and cytosolic stabilization. Cells acquire an elongated phenotype, which relates to RhoA inactivation and loss of E-cadherin expression is accompanied by EMT[408]. In glioma, KITENIN (VANGL planar cell polarity protein 1), a tetraspanin partner, induces expression of the EMT markers N-cadherin, Zeb1, Zeb2, Snail and Slug and expression of the CSC markers CD133, aldehyde dehydrogenase 1 and ephrin receptor B1[409]. Signaling through TIMP-1 (metallopeptidase inhibitor 1) induces in breast cancer in dependence of CD63 Twist1 expression, where a knockdown of Twist1 rescues E-cadherin expression[410]. In PaCa, upregulation of Notch-1 depends on Tspan8, similar effects being not induced by CD151[130]. Instead, in mammary progenitor cells CD151 accounts for nuclear distribution of Slug and represses mammary branching morphogenesis[306], whereas in ovarian cancer the CD151-α3β1 complex represses Slug-mediated EMT and Wnt signaling[411]. Similar, highest level of CD63 in melanoma revealed a significant resistance to undergo an EMT program[412].

The CSC marker CXCR4, too, was described to contribute to EMT. Constitutively active CXCR4, but not wild type CXCR4 induces EMT in mammary carcinoma cells, characterized by upregulation of Zeb1, upregulation of cadherin 11, p120 isoform switching, activation of ERK1/2 and MMP2, but loss of E-cadherin. In 3-dimensional cultures, wt CXCR4 also suffices promoting EMT, which is accompanied by CXCR2, CXCR7, CXCL1, CXCL8, CCL2, IL6 and GMCSF expression. Inhibition of CXCR4 together with MAPK1 or PI3K reversed the EMT phenotype[413]. UHRF1 (ubiquitin-like, with PHD and RING finger domains 1) plays a crucial role in DNA CpG methylation, chromatin remodeling and gene expression. Downregulation of UHRF1 induces Zeb1 and Snail expression accompanied by decreased E-cadherin and increased N-cadherin and vimentin expression. The authors speculate that activation of the CXCR4 signaling pathway is of central importance[414].

EpC is well accepted as a CSC marker, but reports on its contribution to EMT are opposing. One study with breast cancer cells reports on the contribution of EpC in TGFβ1-induced EMT. TGFβ1 treatment induced EpC expression, which promoted EMT and cell migration. EpC overexpression further enhanced TGFβ1-induced EMT. TGFβ1 treatment induces JNK phosphorylation that promoted increased Jun and Fos expression suggesting an important role of EpC in the induction of EMT *via* JNK signaling[415]. Opposing findings were reported for prostate cancer, where EpC was repressed upon induction of EMT. miR-200c and miR-205 are two inducers of MET (mesenchymal-epithelial transition). Re-induction of the epithelial phenotype through miR-200c and miR-205 was accompanied by EpC reexpression[416]. Instead, we reported on unaltered EpC and increased cld7 expression in PaCa and CoCa spheres/holoclones and migrating tumor cells[341]. Recruitment of monomeric EpC into GEM *via* palmitoylated cld7 and EpC cleavage could well account for EpC initiating pronounced EMT induction[273,371]. Furthermore, we and other groups reported on upregulation of GEM-located palmitoylated cld7 in CSC and a pronounced release of the EpC-cld7 complex into TEX[273,361], which promote Snail, Slug and Twist expression[273]. Opposing findings have also been reported, where a knockdown of cld7 induced EMT. A cld7 signature gene profile revealed highly upregulated Rab25, a CoCa suppressor and regulator of polarized cell trafficking in cld7 overexpressing cells. Rab25 silencing counteracted the effects of cld7 expression and increased p-src and Erk1/2 expression[417]. The study did not take into account the engagement of rab25 in vesicle traffic. Further elaborating the recruitment of the EpC-cld7 complex into GEM and exosomes may clarify these seemingly opposing findings.

Finally, CD133 overexpression induces "stemness" properties in PaCa cells and EMT. EMT induction and increased invasiveness are mediated by NFκB activation[418].

Thus, CD44v6, c-Met, Tspan8, α6β4, CXCR4 and CD133 are engaged in promoting EMT. We and others provided evidence for a contribution of an EpC-cld7 complex in EMT. However, this topic is still controversial.

Pancreatic cancer stem cell markers, EMT and miRNA

There is abundant information on altered miRNA profiles in cancer, including CSC and tumor cells in EMT. For more detailed information on miRNA in PaCa excellent reviews are available, besides others in[137,419-422]. Thus, we will mention only a few publications referring explicitly to the mutual impact of CSC markers on miRNA and vice versa.

HA-activated CD44 binds Twist, which supports transcription of miR-10b, which blocks the tumor

suppressor HOXD10 allowing for RhoA and ROK activation with consequences on organization of the cytoskeleton/tumor cell motility as well as apoptosis resistance *via* activation of the PI3K/Akt pathway. Activated CD44 also binds to Nanog, which together with Stat3 translocates to the nucleus and initiates miR-21 transcription, which downregulates the tumor suppressor PDCD4 and promotes expression of survival proteins[423]. HA-activated CD44v3 interacts with Oct4, Sox2 and Nanog, stimulating miR-302 expression, which leads to downregulation of epigenetic regulators and activation of survival proteins[424]. CD44-bound HER2 induces histone deacetylation accounting for transcriptional repression of miR-139, which targets CXCR4, the finding providing a link between upregulated expression of CD44 and CXCR4 in gastrointestinal CSC[325]. Notch-1-induced increased miR-21 and decreased miR-200b, miR-200c, let-7a, let-7b and let-7c expression is accompanied by upregulation of the CSC surface markers CD44 and EpC[402]. Up-regulated miR-155 significantly increases the population of CSCs as well as EMT in liver cancer cells *via* silencing TP53INP1 (tumor protein p53 inducible nuclear protein 1), changes being initiated by TGFβ1 that indirectly regulates TP53INP1 *via* induction of miR-155[425]. miR-34a induces MET *via* down-regulation of Snail by binding to the Snail 3'-UTR, which is accompanied by down-regulation of Bmi1, CD44, CD133, olfactomedin and c-myc. Conversely, Snail and Zeb1 bind to E-boxes in the miR-34a/b/c promoters, which represses miR-34a and miR-34b/c expression. Thus, inactivation of miR-34a/b/c, which is frequent in cancer, can shift the equilibrium of these reciprocal regulations towards EMT[78]. Sonic hedgehog signaling also becomes engaged in EMT by downregulation of miR-200b and let-7c with concomitant upregulation of CSC markers[426]. In CoCa, miR-142-3p targets CD133, Lgr5 (leucine-rich repeat containing G protein-coupled receptor 5) and ABCG2, where Oct4 suppresses miR-142-3, expression being particularly low in CSC-enriched spheres[427]. In PaCa miR-34 is lost in the population of CSC, which is accompanied by Notch and Bcl2 pathway activation, transcription of miR-34 being regulated by p53[428]. However, it should be mentioned that most of these studies were oriented towards therapy and evaluated in first instance the regulation of EMT transcription factors, their reduction expectedly correlating with CSC marker expression, which excludes in several instances a statement on a direct impact of these miRNA on CSC marker expression. A miRNA analysis of rat and human PaCa with downregulation of the CSC markers CD44v6, EpC, cld7 and Tspan8[35,202] confirmed low level miR-34a recovery in CD44v6-competent PaCa and upregulated expression in CD44v6^{kd} PaCa, which is in line with miR-34a targeting CD44[429]. Furthermore, miR-103 transcription is more than two-fold increased in TEX from CD44v6-competent compared to CD44v6-deficient cells. As c-Met supports miR-103 transcription[430], the finding indicates that *via* CD44v6 c-Met also becomes engaged in miRNA transcription and/or posttranscriptional regulation. Finally, CD44v6-related changes are mostly reflected in the TEX miRNA profile such that miRNA reduced in CD44v6^{kd} cells is also lower in TEX from CD44v6^{kd} than CD44v6-competent cells[202]. Tspan8 and cld7 exerted a pronounced effect mostly on miRNA known to be engaged in EMT gene expression. The functional relevance remains to be explored.

In brief, there is evidence for an impact of CSC markers on miRNA expression/repression. miRNA also affects CSC marker expression directly or *via* EMT genes and involved signaling pathways. Still, we are far from having a precise overview of these interlinked networks.

CONTRIBUTION OF PANCREATIC CANCER STEM CELL MARKERS TO TEX

Pancreatic cancer stem cell markers and recruitment of proteins and miRNA into TEX

We already outlined the engagement of Pa-CSC markers in TEX biogenesis, where GEM located Tspan8 plays a decisive role in early endosome formation[124,129]. CD44v6, α6β4, the EpC-cld7 complex and partly CD133 are co-recruited due to enrichment in these tetraspanin-dominated microdomains. According to unpublished findings, palmitoylated cld7 is actively engaged in early endosome traffic towards MVB and the release of ILV as exosomes. Fittingly, Tspan8, α6β4, CD44v6, cld7 and CD133 are enriched in TEX compared to Pa-CSC[162]. Comparative analyses of miRNA in TEX derived from Pa-CSC marker-expressing *vs* -depleted cells confirmed enriched recovery of EMT-related miRNA in Pa-CSC TEX and indicated an additional loss, respectively, enrichment of several miRNA related to the metastatic process, which still requires elaboration of the routing into TEX[202]. Similar findings were reported at the proteome level by the group of Rak. TEX from A431 cells that were driven into EMT exhibit profound qualitative differences in their proteome compared to TEX from the parental cells, but also differed from the A431-EMT cells with 30 proteins related to growth, signaling and motility being uniquely recruited into A431-EMT-derived TEX. The authors propose that changes in the cellular differentiation status translate into unique qualitative rearrangements in the cargo of TEX[431]. Along this line, the oncoprotein latent membrane protein 1 (LMP1) recruits HIF1α into TEX of nasopharyngeal carcinoma. TEX HIF1α remains function-competent in recipient cells, LMP1$^+$ and HIF1a$^+$ TEX initiating EMT with reverting the expression of E- and N-cadherins in TEX target cells[432].

Contribution of pancreatic cancer stem cell markers to TEX binding and uptake

The power of exosomes relies on their ubiquitous presence, their particular protein, mRNA, ncRNA and DNA profile and their most efficient binding and/or transfer in target cells. Information on the latter aspect, though a prerequisite for clinical translation, is still limited.

Binding of PaCa TEX to the extracellular matrix (ECM) varies with the adhesion molecule profile of the exosomes. Thus, high CD44 expression is accompanied by HA binding and high α6β4 expression by laminin (LN) 332 binding, the findings being confirmed by antibody blocking[433]. Myeloma cell line- and myeloma patient-derived TEX revealed fibronectin as key heparan sulfate-binding ligand and mediator of TEX-cell interactions, where removal of heparan sulfate from TEX dramatically inhibiting TEX-target cell interactions. The authors describe a dual role of heparan sulfate in TEX-cell interaction. TEX heparan sulfate captures FN. Concomitantly it acts as a FN receptor on target cells[434]. Live-cell imaging also revealed a critical role of FN and integrin cargo sorting into TEX, which promoted persisting cell motility[435]. In line with the latter report, there is abundant evidence for the engagement of integrins in exosome binding. During reticulocyte maturation, integrin α4β1 is recruited into exosomes, which bind to FN. The interaction depends on divalent cations and is inhibited by an α4-specific antibody, the authors speculating on functional activity of exosomal α4β1 by binding to endothelial cells through CD54[436]. B cell exosomes also interact with the ECM and fibroblasts *via* β1 and β2 integrins, antibody blocking studies confirming engagement in adhesion to collagen-I and FN and to activated fibroblasts *via* TNFα[437]. TEX of a PaCa transiently interfered with leukocyte migration. This is due to TEX occupying the migration-promoting receptors CD44, α4, CD62L and CD54[438]. T cells, too, recruit dendritic cell (DC) exosomes not *via* the T cell receptor complex, but *via* leukocyte function-associated antigen-1 (LFA1)[439]. Most impressive has been the elucidation that TEX integrin profiles account for the organ preference of metastasis initiated by formation of a premetastatic niche. A proteome analysis revealed distinct integrin expression patterns in subpopulations of TEX. Notably, exosomal integrins α6β4 and α6β1 were associated with lung metastasis, whereas exosomal integrin αvβ5 was linked to liver metastasis. A blockade of α6β4 or αvβ5 decreased TEX uptake, as well as lung, respectively, liver metastasis. Furthermore, TEX from mouse and human tumors are preferentially taken up by resident cells at their predicted metastatic destination, *i.e.,* TEX of tumors metastaizing to the lung are taken up by lung fibroblasts and epithelial cells, TEX of tumors that metastasize to the liver are captured by Kupffer cells and TEX from tumors metastasizing to the brain are recovered in brain endothelial cells (EC). Finally, TEX integrins displayed functional activity, activating Src phosphorylation and pro-inflammatory S100 gene expression after uptake by resident cells[440]. These studies confirmed and expanded our previous work that described distinct TEX integrins to target *e.g.,* EC, fibroblasts or bone marrow cells, where the selectivity of TEX uptake is guided or, at least, facilitated by the engagement of protein complexes at the exosome and the target cell membranes[441]. In fact, only defined tetraspanin-integrin complexes are taken up by selected target cells. Importantly, TEX uptake proceeds *via* binding to internalization prone microdomains[129]. The constitutively high expression of GEM-located tetraspanins and the multitude of associated molecules, with a preference for integrins[107], favors our suggestion. Besides supporting the selectivity of binding and uptake, the engagement of complexes of TEX receptors and target cell ligands favors induction of signal transduction as *e.g.,* known for T cell activation, which requires engagement of the T cell receptor and accessory molecules that interact with MHC and costimulatory molecules on DC[442]. So far we supported our hypothesis by elaborating that TEX expressing Tspan8 and α4β1 preferentially target EC and promote EC and EC progenitor activation[247], where exosomes from Tspan8 and α4 transfected fibroblasts exhibited a comparable target cell selectivity[129]. Instead, PaCa TEX expressing Tspan8 and α6β4 preferentially bind and are taken up by lymph node stroma cells and lung fibroblasts[130], lymph nodes and lung being the exclusive metastatic sites for this PaCa[443].

Taken together, for GEM-derived TEX there is strong evidence for preferential uptake by corresponding, internalization prone membrane microdomains. Furthermore, the work by the Lyden group depicting TEX integrins accounting for metastasis organ preference[440] and our work on the engagement of tetraspanin-integrin complexes facilitating selective targeting[129,130,247,443] provides a solid base for defining GEM-derived TEX target structures. Comparable studies for TEX uptake *via* phosphatidylserine receptors, by phagocytosis, macropinocytosis and membrane fusion[444-449] are still awaited (Figure 6A).

TEX, PANCREATIC CANCER STEM CELL MARKERS AND THE CROSSTALK WITH THE HOST

In advance of reviewing the impact of Pa-CSC markers on angiogenesis and the premetastatic niche, we want to refer to excellent reviews that elaborate the impact of TEX on tumorigenicity[98,450], tumor growth related thrombosis[451-453], hematopoiesis[199,454,455] and mature leukocytes, including all components of the immune system[456-463], where particularly the Pa-CSC TEX

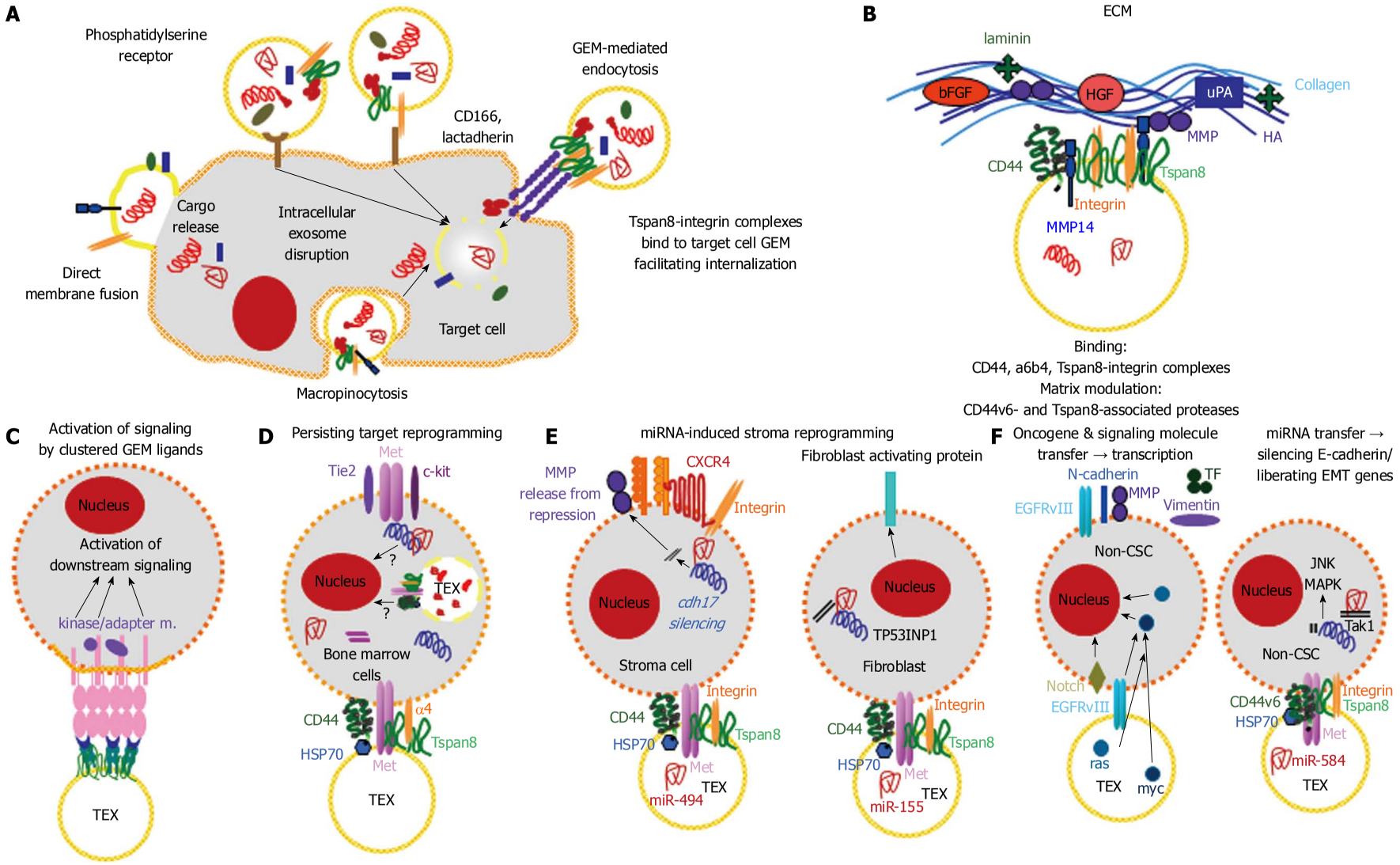

Figure 6 Contribution of exosomal cancer stem cell markers to target selection, binding, uptake and target modulation. A: Exosomes uptake by cells can proceed *via* membrane fusion, macropinocytosis, receptor ligand binding. GEM-derived exosomes bind to complexes of ligands located in internalization prone membrane microdomains, which increases selectivity of uptake and facilitates uptake; B: Binding to the ECM is facilitated by the Pa-CSC markers α6β4 and CD44v6. CD44v6- and Tspan8-associated proteases facilitate matrix degradation; C-E: There are multiple pathways whereby TEX affect target cells, only selected examples are shown: Signal transduction can be initiated by clustering GEM ligands; in progenitor cells, *e.g.*, in the bone marrow, activation of signaling molecules can initiate a shift towards differentiation; the transfer of TEX miRNA can initiate release from repression by the miRNA target or tumor suppressor RNA can become silenced such that resting mesenchymal cells turn into an activated phenotype; F: EMT was induced in Non-CSC by the transfer of oncogenes, activation of EMT-related transcription factors or miRNA blocking transcription of RNA engaged in epithelial stage maintenance. CSC: Cancer stem cells; GEM: Glycolipid-enriched microdomains; ECM: Extracellular matrix; EMT: Epithelial mesenchymal transition; HA: Hyaluronan; TEX: Tumor exosomes.

markers CXCR4, CD44v6 and c-Met may play a role.

Contribution of pancreatic cancer stem cell TEX markers to angiogenesis

There is ample evidence on the engagement of TEX in angiogenesis. It was first described for TEX of a non-metastatic rat pancreatic cancer that induced overshooting angiogenesis resulting in a lethal consumption coagulopathy[464]. TEX were preferentially taken up by EC and EC progenitors, binding and uptake requiring a Tspan8-α4β1 complex. Notably, by exchange of α4β1 by α6β4, TEX did not bind to EC and overshooting angiogenesis was prevented[246]. Uptake of Tspan8-α4β1 TEX by EC resulted in upregulation of tissue factor, VEGFR1, CXCL5, CCR1 and HMOX1 as well as of Tpan8 and CD31. Depending on the culture condition, progenitor cells could also be driven into smooth muscle cell differentiation[250]. We are not aware on further studies on Pa-CSC TEX markers in angiogenesis. Therefore, and as TEX-induced angiogenesis meanwhile is described in nearly all tumor entities, we refer to some reviews on TEX-initiated signal transduction in EC as well as on the engagement of transferred miRNA[152,465-467]. However, we want to mention that to our knowledge, the first report on exosomes induced angiogenesis referred to platelet-derived exosomes[468], which we interpret as an additional evidence that CSC take over physiological programs including the use of exosomes.

Pancreatic cancer stem cell markers, TEX and the crosstalk with the host

Paving the way for metastasizing tumor cells: Exosomes are rich in function-competent proteases. Exosome proteases can modulate the exosome protein profile, the ECM and/or target cells. Besides others, MMP2, 7, 9, 14, ADAM10, 15, 17, ADAMTS1, 13 and several dipeptidases were recovered in TEX[469,470]. These TEX proteases can modulate the TEX protein profile, which includes the Pa-CSC markers CD44, shedded by ADAM10, MMP14 and MMP9[471-473], and EpC, shedded by ADAM14[474]. Besides this internal regulation of CD44v6 and EpC expression in TEX, frequently accompanied by release of the ICD, which in turn promotes transcription of genes promoting tumorigenicity and metastasis[187,349,350], the association of TEX CD44v6 and Tspan8 with proteases severely affects the host matrix. The modulated matrix, in turn, facilitates metastasizing tumor cell migration towards the metastatic organ.

HA is the most abundant ECM protein, with TEX binding *via* CD44[170,475]. Notably, TEX also contain HAS and Hyal and were described to be HA-coated. The authors speculate that TEX serve as special vehicle for HA, where exosomal HA itself or associated molecules could create an environment supporting cancer cell invasion and metastasis[476]. In concern about the contribution of CD44v6, we noted in some, but not all tested TEX of PaCa-CD44v6^{kd} lines a reduction in HAS3 and upregulated expression of Hyal1. In addition, CD44v6-competent, but not CD44v6-deficient TEX-modulated HA promotes tumor cell migration[100].

CD44 regulates expression and cooperates with several proteases[195,196,477], where MMP2, MMP3, MMP7, MMP9, MMP14 as well as ADAM10 and ADAM17 are recovered in PaCa TEX and MMP9, MMP14 and ADAM17 are strongly downregulated in TEX of CD44v6^{kd} lines[433]. These proteases coimmunoprecipitate with CD44v6 in PaCa-TEX, indicating their recruitment into TEX *via* associated CD44v6[433]. CD44v6-competent PaCa TEX degrade coll Ⅰ, coll Ⅳ, FN, LN111 and, less pronounced LN332, matrix degradation by PaCa TEX being accompanied by pronounced tumor cell migration and invasion[433]. Similar findings were reported for MMP14, where the authors suggest that coll IV, which is not a MMP14 target, becomes degraded by MMP14-activated proMMP-2[470]. Finally, host matrix degradation by CD44v6-competent TEX is accompanied by activation of proliferation and survival signals[433]. This is likely due to liberation of growth factors, chemokines and additional proteases from the degraded matrix as well as by cleavage of additional targets by the TEX proteases[207,478].

Tspan8 also associates with proteases, particularly MMP9 and TACE[245] and Tspan8-associated proteases are recovered in PaCa TEX, where they degrade the host matrix[130]. The efficacy of Tpan8-expressing TEX appears to exceed that of CD44v6^{+} TEX, which likely is due to the strong association of tetraspanins with integrins[241,242]. Thereby matrix protein binding becomes focalized, strengthening the efficacy of matrix degradation. This accounts in particular for LN332 degradation. Due to its association with TACE, Tspan8 also contributes to FN degradation[130]. Though we focused on the contribution of the Pa-CSC marker Tspan8 in matrix modulation, other TEX tetraspanin-protease complexes also contribute to host matrix modulation[130,460,479-484].

In brief (Figure 6B), TEX proteases modulate the ECM thereby creating a path for migrating PaCa cells and a milieu favoring tumor cell migration, angiogenesis and premetastatic niche establishment. The Pa-CSC markers CD44v6 and Tspan8 essentially contribute to the process of matrix modulation by TEX due to their engagement in protease transcription (CD44v6), TEX biogenesis (Tspan8) and their association with proteases in GEM (CD44v6 and Tspan8).

Preparing a niche: TEX uptake remodels recipient non-tumor cells towards driving tumor growth. After the first description of a premetastatic niche[96], the engagement of TEX soon became obvious, which we were the first to describe for a rat PaCa-CD44v6^{kd} line that had lost the capacity of the parental line to metastasize, but regained metastatic capacity, when rats were pretreated with TEX of the parental

line[100]. Similarly, renal CSC expressing the SC marker CD105 release TEX that trigger angiogenesis and greatly enhanced lung metastases. The $CD105^+$ TEX are characterized by sets of mRNAs and microRNAs supporting angiogenesis and tumor progression[95]. Also melanoma TEX home to sentinel lymph nodes imposing molecular signals that support melanoma cell recruitment, extracellular matrix deposition, and vascular proliferation, thereby facilitating lymphatic metastasis[485]. A proteome analysis of CoCa TEX uncovered enrichment particularly of metastasis-promoting factors (c-Met, S100A8, S100A9, tenascinC), of signal transduction molecules (ephrinB2, jagged1, src, TRAF2 and NCK interacting kinase <TNIK>), and lipid raft/lipid raft-associated components (caveolin, flotilin1 and 2, CD133) in TEX derived from a metastatic line. An additional key finding was the recovery of EpC-cld7 and TNIK-rap2A complexes in TEX[132] (Figure 6C). The mode of TEX-induced premetastatic niche formation was also elaborated using TEX from a metastatic and a non-metastatic melanoma line. TEX from highly metastatic melanoma line increased the metastatic behavior of primary tumors by affecting bone marrow progenitors through c-Met. Melanoma-TEX reprogrammed bone marrow progenitors towards a provasculogenic phenotype defined by c-Kit, Tie2 and c-Met expression. Reduced c-Met expression in TEX diminished the pro-metastatic behavior of bone marrow cells. $c\text{-}Met^+/c\text{-}Kit^+/Tie2^+$ bone marrow progenitors were also recovered in patients with metastatic melanoma. Premetastatic niche promoting TEX were high in α4, HSP and c-Met. The authors conclude that metastasizing melanoma TEX "home" to the bone marrow, where they reprogram bone marrow cells to support tumor growth and metastasis[486]. The pathway of persisting reprogramming remains to be elaborated. However, it is conceivable that TEX contain transcription factors inducing a differentiation switch in this non-differentiated cells. In a mouse model of PaCa that metastasizes to the liver, TEX induce liver premetastatic niche formation and increase liver metastatic burden. TEX uptake by Kupffer cells promoted TGFβ and FN secretion. The fibrotic microenvironment enhanced recruitment of bone marrow-derived macrophages. The authors report on high macrophage migration inhibitory factor (MIF) expression in PaCa TEX, where a MIF blockade prevented liver pre-metastatic niche formation and metastasis. High MIF expression in TEX was also seen at an early stage of PaCa growth in patients that developed liver metastasis[101]. Evidence for the transfer of c-Met and for TEX stimulated c-Met-signaling in target cells fits to the CD44v6-c-Met complex recovery in Pa-CSC TEX[202,433]. Activation of src also may well proceed *via* CD44v6-c-Met as well as *via* integrin tetraspanin complexes[130,207]. The high recovery of inflammatory HSP in TEX could be due to the association with Tspan8 and could strengthen the efficacy of the frequently described upregulation of chemokines and mostly immunosuppressive cytokines as well as of inflammatory complement components and S100 in Pa-CSC TEX[487-490]. However, for the latter set of molecules a link to Pa-CSC markers remains to be defined (Figure 6C and D).

The miRNA content of TEX from $CD44v6^{kd}$, $Tspan8^{kd}$ and $cld7^{kd}$ cells differ from that of wt cell-derived TEX. Exploring the impact of CD44v6-linked miRNA transferred into stroma cells revealed 18 mRNA downregulation. From the total TEX miRNA, 60% could potentially be engaged in targeting these 18 mRNA. We focused on abundant miR-494, potentially targeting MAL and cdh17, and miR-542-3p, targeting cdh17 and TNF receptor associated factor 4 (TRAF4). MAL can contribute to differentiation and apical sorting[491] and cdh17 to tumor growth/Wnt signaling[492]; TRAF4 exerts morphogenetic functions[493]. Lymph node stroma transfection with these miRNAs was accompanied by down-regulation of the predicted target(s). Significant up-regulation of mRNA in exosome-treated LnStr pointed toward mRNA up-regulation through miRNA silencing regulatory mRNA. Cdh17 represses MMP2 and MMP9 expression[494] and down-regulation of cdh17 in miR-494 and miR-542-3p transfected stroma cells was accompanied by MMP2, MMP3 and MMP14 up-regulation[202]. In another study with PaCa TEX, the authors found down-regulation of exosomal miR-155 and miR-196a and upregulation of miR-17-5p, upregulation correlating with metastasis and advanced tumor stages[33]. Further controlling for the impact of miR-155 in PaCa TEX revealed normal fibroblasts to become converted into CAF after uptake of miR-155 containing TEX. TP53INP1 is a target of miR-155 in fibroblasts and TP53INP1 protein downregulation can contribute to fibroblasts activation[495] (Figure 6E).

Without question TEX account for preparing a niche for migrating tumor cells. In PaCa TEX, there is strong evidence for a direct engagement of CD44v6, c-Met, integrins and Tspan8-associated integrins. An active contribution of cld7, the EpCAM-cld7 complex, CD133 and CXCR4 remains to be explored. According to the current state of knowledge, binding-induced as well as uptake-initiated signal transduction and the transfer of miRNA cooperate in target cell modulation.

Exosomal pancreatic cancer stem cell markers and the crosstalk with non-cancer stem cells

CSC TEX also modulate other tumor cells *via* protein, mRNA and miRNA transfer[496,497].

One of the first and most impressive reports on TEX-uptake being critical in tumor growth stimulation describes the intercellular transfer of the oncogenic receptor EGFRvⅢ *via* TEX to glioma cells, lacking this receptor, which causes transformation of indolent glioma cells[133]. The oncogenes Ras, Myc, SV40T also induce signaling and gene expression[136,140,498]. Amphiregulin is an EGFR ligand. Compared to recombinant

protein, TEX-associated amphiregulin increases tumor invasiveness 5-fold. The finding strongly suggests the transfer of additional messages *via* TEX[499]. In lung cancer TEX miR-21 and miR-29a act a TLR ligand and function as agonist. This leads to NFκB activation and IL6 and TNFα secretion promoting metastasis[500]. A set of miRNA, including miR-584, miR-517c, are not detected in the donor cell, but are highly enriched in hepatocellular carcinoma TEX. A potential target of these miRNA is TGFβ activated kinase 1, which activates JNK and MAPK pathways and NFκB. In cocultures, these TEX miRNA promote anchorage-independent growth and apoptosis resistance[501]. Apoptosis resistance can also rely on the transfer of multidrug resistance (MDR)1[502], which is enriched in TEX[503].

Furthermore, after oncogenic H-Ras-induced EMT, the TEX profile significantly changes, including TGFβ, TNFα, IL6, TSG101, Akt, ILK1, β-catenin, hepatoma-derived growth factor, casein kinase Ⅱ, annexinA2, α3 integrin, caveolin and MMPs, the authors pointing out that the protein content of EMT TEX likely can induce EMT in recipient cells[473]. TEX also contain EBV-derived LMP1, which modulates together with HIF1α EMT marker expression in recipient cells[504]. TEX from human CSC-enriched CoCa lines can induce EMT in the CSC-depleted population. There is a strong induction of Notch, N-cadherin becomes upregulated and E-cadherin downregulated[273]. In a rat PaCa, CSC TEX promote Notch and Snail transcription depending on the presence of Tspan8[130] (Figure 6F). Still being at the descriptive level, it is obvious that CSC TEX can confer CSC features towards non-CSC including EMT, where TEX components work in concert.

Thus, Pa-CSC TEX markers are essential components for TEX targeting and account for selective responses, *e.g., via* src activation. For other responses, including the impact of miRNA, a contribution of Pa-CSC markers to the recruitment into TEX was repeatedly demonstrated. Though information on the contribution of exosomal Pa-CSC markers on target cell activation/reprogramming is still limited, available data convincingly demonstrate the engagement of Pa-CSC markers in TEX assembly, binding and message transfer.

CONCLUSION

CSC markers have long been considered as a tool for CSC enrichment and diagnosis. We here demonstrate for the Pa-CSC markers CD44v6, c-Met, Tspan8, α6β4, EpCAM, cld7, CXCR4 and CD133 that these markers contribute in maintaining CSC features essential for tumor persistence and progression. These Pa-CSC markers are required to (1) maintain the CSC status by their engagement in signal transduction, transcription including miRNA and repression of tumor suppressor genes; (2) establish a stem cell niche including a premetastatic niche by affecting *via* ligand binding target cell activation and message transfer; (3) support EMT by gene transcription and/or silencing; and (4) tumor cell migration and invasion *via* associated integrins and proteases.

The power of these markers relies on their residence in GEM, which allows for concerted activity and the engagement in TEX biogenesis and delivery. The CSC marker panel being maintained in TEX guarantees CSC to prepare the host for their maintenance at distant sites.

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