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PII: S0304-419X(18)30055-6
DOI: doi:10.1016/j.bbcan.2018.04.005
Reference: BBACAN 88216

To appear in:

Received date: 15 March 2018
Revised date: 13 April 2018
Accepted date: 14 April 2018

Please cite this article as: J. Ignacio Casal, Rubén A. Bartolomé , RGD cadherins and α2β1 integrin in cancer metastasis: A dangerous liaison. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Bbacan(2018), doi:10.1016/j.bbcan.2018.04.005

RGD cadherins and α2β1 integrin in cancer metastasis: A dangerous liaison

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Keywords: Cadherin 17, VE-cadherin, CDH6, α2β1 integrin, RGD motif, Type IV collagen, Metastasis, Therapeutic antibodies

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ABSTRACT

We propose a new cadherin family classification comprising epithelial cadherins (cadherin 17 [CDH17], cadherin 16, VE-cadherin, cadherin 6 and cadherin 20) containing RGD motifs within their sequences. Expression of some RGD cadherins is associated with aggressive forms of cancer during the late stages of metastasis, and CDH17 and VE-cadherin have emerged as critical actors in cancer metastasis. After binding to α2β1 integrin, these cadherins promote integrin β1 activation, and thereby cell adhesion, invasion and proliferation, in liver and lung metastasis. Activation of α2β1 integrin provokes an affinity increase for type IV collagen, a major component of the basement membrane and a critical partner for cell anchoring in liver and other metastatic organs. Activation of α2β1 integrin by RGD motifs breaks an old paradigm of integrin classification and supports an important role of this integrin in cancer metastasis. Recently, synthetic peptides containing the RGD motif of CDH17 elicited highly specific and selective antibodies that block the ability of CDH17 RGD to activate α2β1 integrin. These monoclonal antibodies inhibit metastatic colonization in orthotopic mouse models of liver and lung metastasis for colorectal cancer and melanoma, respectively. Hopefully, blocking the cadherin RGD ligand capacity will give us control over the integrin activity in solid tumors metastasis, paving the way for development of new agents of cancer treatment.

1. Introduction

The invasion-metastasis cascade is a complex multi-step process. In order to form distant metastasis, tumor cells need to detach from the primary tumor, undergo intravasation, survive circulation, extravasate in the parenchyma of distant organs and proliferate in a hostile organ microenvironment [1]. This last step of "colonization" is probably the least efficient step in the invasion-metastasis cascade but is the most determinant in the final outcome for the cancer patient. In distant organs, tumor cells require adaptation to the microenvironment ("soil") to anchor, grow and proliferate. There is a clear organ-specific pattern of metastasis for many tumors, i.e. pancreatic cancer, uveal melanoma and colorectal cancer metastasize preferentially to the liver; prostate cancer, preferentially to bone; and breast cancer, to different organs [1]. Liver is a major site of metastasis for human cancers, yet the factors that regulate tumor cell adhesion, proliferation and survival in liver metastasis remain uncertain. Only a small percentage of micrometastasis-positive patients will ever develop metastatic relapse [2]. To succeed in developing large metastasis, a combination of adhesion and proliferation abilities is necessary, which cells probably develop by epigenetic regulation and selective expression/repression of multiple genes. These challenges are organ-specific and probably require different mechanisms for different microenvironments. Therefore, targeting colonization mechanisms of metastasis is a critical key for improving survival of cancer patients.

Metastasis depends on different growth factors, receptors, proteases, chemokines and cellular adhesion molecules [3]. Adhesion molecules include cadherins, integrins and immunoglobulin superfamily molecules [4]. Adhesion molecules can mediate adhesion between cells (i.e. cadherins and integrins) or to components of the extracellular matrix, such as laminins, collagens and fibronectin (i.e. integrins) [5]. In this review, we will focus on five human cadherins that contain RGD motifs—two 7D cadherins (cadherin 17 [CDH17] and cadherin 16

[CDH16] and three type II cadherins (VE-cadherin [CDH5], cadherin 6 [CDH6] and cadherin 20 [CDH20])—and the α2β1 integrin [6]. Recently, we proposed that two of these RGD-motif cadherins (CDH17 and VE-cadherin) play a critical role in liver and lung colonization metastasis by promoting adhesion, invasion and proliferation of melanoma and colorectal cancer cells [6, 7]. These cadherins function as α2β1 integrin ligands that activate the integrin signaling pathway. This characteristic implies a paradigm change, as it demonstrates the capacity of α2β1 integrin to function also as an RGD receptor in cancer metastatic cells. Blocking the binding of RGD cadherin to α2β1 integrin in different solid tumors presents a promising therapeutic window for inhibiting metastatic colonization. In this article, we describe the components of this unusual complex.

2. Overview of cadherins

Traditionally, cadherins are glycoproteins that mediate calcium-dependent cell-cell adhesion in early vertebrate embryo development and epithelial tissues [8]. However, cadherins are promiscuous proteins that participate in many other specialized functional features [9]. The cadherin superfamily consists of 115 genes in humans that can be classified into a number of families: cadherins in the strictest sense (29 genes); the closest known relatives of cadherins, the flamingo cadherins (3 genes); the clustered protocadherins (protocadherins α, β and γ; 54 genes); the non-clustered protocadherins (protocadherins δ; 12 genes); several divergent small families (Fat1-4, dachsous cadherin 1 and 2, cadherin-related 1–5, calsyntenins 1-3); and three isolated genes (Ret, CDH23 and PCDH15). The phylogenetic classification of cadherin superfamily has been determined (see [10] for a review).

The cadherin family is formed by several subfamilies: type I or classical cadherins, type II or atypical cadherins, desmocollins, desmogleins, 7-domain cadherins and the isolated CDH13 and CDH26 [10]. The type I cadherin group includes the canonical E-cadherin (CDH1) as well as CDH2-4 and CDH-15. Structurally, the cadherins of this subfamily are composed by a long

prodomain followed by five extracellular calcium-binding cadherin domains and a cadherin cytoplasmic domain, which is linked to the actin cytoskeleton through the catenins (α-, β-, and p120-catenin). A tryptophan in position 2 of the N-terminal cadherin domain is critical for the cross-linking between cadherins. Type II cadherins have the same structure of type I except for having a shorter prodomain. In addition, for homotypic binding, these cadherins use two tryptophans, in positions 2 and 4. This is the largest subfamily, with 13 members (CDH5-12, CDH18-20, CDH22 and CDH24). The two members of the 7-domain subfamily are CDH17 and CDH16, which present seven cadherin domains in the extracellular region. However, they have a very short cytoplasmic tail, of only 18–22 amino acids, that cannot bind to catenins. CDH13 (H-cadherin or T-cadherin) has 5 cadherin domains but lacks the cytoplasmic domain; it is the only member of the cadherin family anchored to the cell membrane by a GPI moiety. In contrast, the poorly studied CDH26 has only 4 cadherin domains but a long cytoplasmic region. Recently, it was identified as a ligand to β7 integrins [11].

Desmocollins (DSC1-3) and desmogleins (DSG1-4) are cadherins involved in desmosomes and robust cell-cell adhesions present in epithelia and heart junctions (intercalated discs) subjected to mechanical strain. Both types of cadherins are linked to intermediate filaments through plakoglobin, desmoplakin, plectin and armadillo proteins plakophilins 1-3 [12]. Desmocollins have a structure quite similar to type I cadherins. In contrast, desmogleins have only 4 cadherin domains and a long cytoplasmic region, which includes several (2 to 6) desmoglein repeats following the typical cadherin cytoplasmic domain [13].

The main physiological function of cadherins is to assist in the sorting of tissue-specific differentiated cells during the development through their homotypic interactions, as each cadherin tends to be expressed at the highest levels in distinct tissue types during development [14]. In addition, they play a prominent and essential role in early development of embryonic stem cells [15, 16]. In adult tissues, cadherins play a major role in stabilizing

epithelial tissue through the cell adherens junctions and desmosomes, and in establishing and maintaining the epithelial cell polarity. Thus, cadherins regulate the orientation of the plane of cell division, allowing directional expansion of tissues. Furthermore, cadherins are important in neurite outgrowth and guidance, axon elongation and synapse formation [14]. In addition, cadherins are involved in cell signaling and mechano-transduction [9].

Focusing on cancer biology, cell-cell adhesion undergoes different changes in signaling, loss of contact inhibition, cell migration and stromal interactions during metastasis [17]. Cadherins play a major role in these changes. E-cadherin (also known as CDH1) is the prototype cadherin and the most intensively studied by far, due to its role in the epithelial-mesenchymal transition (EMT) during cancer progression [18]. The function of classical cadherins (e.g., CDH1) in cancer is quite complex and generally involves the disruption of the cadherin-mediated intercellular adhesion usually by the repression of E-cadherin and the release of oncogenic β-catenin (nuclear factor in Wnt signaling) and other catenins [19]. In some cancer cells, CDH2 and CDH3 expression is associated with CDH1 repression, forming the so-called cadherin switch, after mesenchymal transition [20]. In contrast to E-cadherin, in many cancer types, the overexpression of cadherins triggers the activation of signaling pathways leading to proliferative, anti-apoptotic and/or invasive responses in the tumor cells (see [21] for a review). Recently, integrin-binding RGD motifs have been described for both 7D cadherins, CDH17 and CDH16, as well as three type II cadherins, CDH5 (vascular-endothelial [VE]-cadherin), CDH6 (fetal kidney [K]-cadherin) and CDH20 [6]. In fact, CDH5 contains two RGD motifs in primates. For brevity, we will henceforth to refer to these five cadherins as RGD cadherins.

3. RGD cadherins

3.1 Cadherin 17

CDH17 and CDH16 belong to the family of seven domain (7D) cadherins. CDH17, also known as liver-intestine cadherin (LI-cadherin), is characterized by an amino-terminal duplication of the first two cadherin repeats [10] and the presence of a truncated cytoplasmic domain that lacks the two armadillo-binding domains present in the classical type I cadherins [10]. This short cytoplasmic domain (18 amino acids) is not related to other cadherins and seems not to interact with catenins or cytoskeleton proteins [22]. CDH17 contains seven N-glycosylation sites [23]. Differences in cellular glycosylation make its apparent molecular weight highly variable, ranging from 90 to 120 kDa in different cell lines. CDH17 is expressed in mice and humans almost exclusively in epithelial cells of both embryonic and adult small intestine and colon, with no detectable expression in the liver (see [24] for a review). CDH17 localizes to the basolateral domain of fetal hepatocytes and enterocytes, where it mediates intercellular adhesion with cadherin molecules in other neighboring cells, forming a “molecular zipper”, in a $Ca^{(2+)}$-dependent manner to maintain tissue integrity in epithelia [23, 25]. Given the non-dependence on cytoplasmic interactions for maintaining cell adhesion, CDH17 might play an important role in regulating cell-cell contacts when classical cadherin-mediated adhesion is disrupted, such as in cancer cells that have lost E-cadherin-mediated adhesion [26]. Whereas CDH17 is localized almost exclusively in cholesterol-rich fractions (“lipid rafts”), E-cadherin is excluded from these membrane fractions [27]. This localization may have important implications for cell signaling, as lipid rafts are used for integrin localization and function [28]. Besides the preferential intestinal expression, CDH17 (also named as BILL-cadherin) is also expressed in memory B lymphocytes that reside in the marginal zone of the spleen [29], where they have a role in the survival and proliferation of long-term memory B cells [30]. However, the exact role of CDH17 in human memory B cells remains unclear. We speculate that CDH17 might facilitate the anchoring of memory B cells to the spleen.

CDH17 mutant mice have been created by removing exons 16–18, which encode the transmembrane and cytoplasmic domains [31]. Homozygous mutant animals, still able to

produce a soluble form of CDH17, are viable and fertile. CDH17 expression is regulated by the intestine-specific caudal-related homeobox transcription factor CDX2. CDX2 plays a key role in intestinal development and differentiation. In primary colorectal cancers and intestinal metaplasia of the stomach, CDX2 and CDH17 expression are highly correlated in a positive way as CDX2 promotes CDH17 expression [26]. CDH17 is highly expressed in hepatocellular carcinoma [32-34], gastric cancer [35, 36], pancreatic cancer [37, 38]–and particularly in the exocrine-like subtype of pancreatic ductal adenocarcinoma [39], esophagus carcinoma, neuroendocrine tumors [40, 41] and colorectal cancer [26, 38, 42, 43]–with 96% of tumor samples showing expression of this molecule [38] (**Table 1**). Different studies have described a clear association of high expression of CDH17 with either lung [42] or liver metastasis in human colon cancer [44], in which it correlates with poor prognosis [45]. CDH17 promotes liver colonization and metastasis in orthotopic mouse colorectal cancer models after intra-splenic injection by interaction with α2β1 integrin (see below) [6, 45]. The fact that CDH17 is expressed at relatively low levels in regional lymph nodes as well as in poorly differentiated colon cancer tumors [46, 47] introduced some controversy about CDH17 expression in colorectal cancer. It is now well established that well-differentiated colorectal cancer tumors express abundant levels of CDH17, while poorly differentiated ones do not express CDH17. Indeed, loss of CDX2 expression is a characteristic of some poorly differentiated colon carcinomas [26]. This low CDX2/CDH17 expression correlates with the low expression of α2β1 and α3β1 integrin in moderate and poorly differentiated colorectal adenocarcinomas [48].

In hepatocarcinoma, loss of CDH17 expression was associated with Wnt signaling inactivation and a significant reduction of total and nuclear β-catenin and the phosphorylated form of GSK-3β [32]. Although β-catenin was also present in the CDH17-associated proteomic network in colorectal cancer cells [45], it is unclear if it directly associates to CDH17 or associates via other proteins, such as galectin 3, which was found to cluster with CDH17 in pancreatic ductal adenocarcinoma [37] and colorectal cancer [45]. Galectin 3 might also participate in the Wnt

signaling pathway alterations induced by CDH17. Other protein associates described for CDH17 in colorectal cancer cells were EPCAM, CD44, SDC1 and α6β4 integrins [45]. These partners might be associated with other important signaling functions for CDH17.

3.2 Cadherin 16

Cadherin 16 (CDH16), also known as kidney-specific cadherin (Ksp-cadherin), is a paralogue of CDH17. Despite their overall structural similarity, CDH16 and CDH17 have quite different expression patterns and functions in tumor biology [21]. Whereas CDH17 is upregulated, CDH16 is downregulated in tumors. CDH16 expression in epithelial cells is lost in renal cell carcinomas [49] and thyroid carcinomas [50, 51], to be replaced by expression of CDH6 [52], another kidney cadherin containing RGD motifs. Snail, a well-characterized repressor of E-cadherin, suppresses CDH16 expression via direct repression of the kidney differentiation factor HNF-1β, which seems to play a role in fibrosis formation in kidney [53]. The role of Snail in the loss of CDH16 in carcinomas, and its replacement by CDH6, remains to be investigated. We speculate that functional differences between CDH16 and CDH17 might be related with the different properties of the RGD motif and their flanking sequences in each cadherin (see below).

3.3 VE-cadherin (CDH5)

VE-cadherin, also known as CDH5 or CD144, is a type II cadherin mainly expressed in endothelial adherens junctions. Therefore, most of the VE-cadherin studies have been related to its role in endothelial cells (see [54] for a recent review). VE-cadherin plays a central role in vascular connections, vascular integrity and permeability and promotes homotypic cell-to-cell adhesion [55]. VE-cadherin contributes to cell polarity, vascular tubulogenesis and rearrangement of the cytoskeleton through its multiple intracellular partners in endothelial cells. Intracellular association to β-, γ- and p120-catenin promotes binding to the actin cytoskeleton, whereas association to plakoglobin (γ-catenin) and desmoplakin provides a link

to intermediate filaments [56]. Mice deficient in VE-cadherin, or expressing truncated VE-cadherin, die in mid-gestation from severe vascular defects, involving endothelial apoptosis and disrupted survival signaling pathways [57]. Through different interactions with transcription factors, VE-cadherin can either repress or stimulate gene transcription [54]. In endothelial cells, VE-cadherin promotes negative signals to switch the cells to a quiescence state. VE-cadherin is also present in the tumor endothelium, and VE-cadherin–specific antibodies have been described to block angiogenesis and tumor growth [58].

The role of VE-cadherin in cancer cells of non-endothelial origin is much less characterized, but seems to be opposite to the role in endothelial cells, as VE-cadherin–positive cancer cells are more proliferative and invasive. Aberrant expression of VE-cadherin was first detected as being involved in vasculogenic mimicry (the ability to form novel blood vessel-like structures) in uveal melanomas [59, 60] and other tumors, such as small cell lung cancer [61], osteosarcoma, ovarian cancer [62] and glioblastoma [63]. Vasculogenic mimicry is associated with shorter patient survival. Such vascular channels may function as blood vessels, contain erythrocytes and may contribute to the perfusion of the tumor tissue. Aggressive uveal melanoma cells express Tie-1 and VE-cadherin but do not express other endothelial markers, such as CD31 and VEGFR2 [60]. In glioblastoma, a subset of glioblastoma stem-like cells differentiates to $CDH5^{+}$ endothelial-like cells to form tubular networks for neoangiogenesis [63]. CDH5 contributes to vasculogenic mimicry by VEGF-independent tumor cell differentiation [64], especially under hypoxic conditions [65]. VE-cadherin is also expressed in Ewing´s sarcoma [66], breast cancer [7, 67], lung cancer [68], highly aggressive cutaneous melanomas [69] and a subset of acute lymphoblastic leukemia cells, in which it contributes to cell survival [70] (**Table 1**). Recently, VE-cadherin has been postulated as a biomarker for gastric cancer [71] and metastatic breast cancer [72], particularly in estrogen receptor–positive breast cancers [73]. VE-cadherin and its glycosylation status may help to distinguish patients with metastatic disease from those who remain metastasis-free.

With respect to signaling capacity in cancer cells, VE-cadherin promotes proliferation of mouse mammary carcinoma cells through Smad2 phosphorylation and the TGFβ signaling pathway [67]. On the other hand, in human cells, loss of VE-cadherin in highly aggressive human melanoma and breast cancer causes a significant loss of malignant traits (proliferation, adhesion, invasion and transendothelial migration) [7]. The proteomic analysis of co-immunoprecipitated proteins with VE-cadherin shows that they are similar in melanoma and breast cancer cells. They include α2β1 integrin, αV integrin and other proteins mainly involved in cell-matrix adhesion, cell-cell adhesion, cell signaling and the actin cytoskeleton, including p120-catenin and plakoglobin through their cytoplasmic domains [7]. VE-cadherin–mediated integrin signaling occurs through specific activation of SRC, ERK and JNK, including AKT in melanoma. Knocking down VE-cadherin suppresses lung colonization capacity of melanoma or breast cancer cells inoculated in mice, while pre-incubation with VE-cadherin RGD peptides promotes lung metastasis for both cancer types [7]. In melanoma and breast cancer patients, CD34-*low* patients with high expression of VE-cadherin exhibit significantly reduced survival times.

It is unclear what role CDH5 overexpression has in metastatic cancer cells beyond the formation of aberrant vascular structures. VE cadherin contributes to maintaining endothelial barrier function. However, this barrier needs to be overcome by metastatic cancer cells during the intravasation and extravasation processes. To do this, metastatic cells promote changes in endothelial cells, including reorganization of the cytoskeleton [74]. Attachment of the invasive breast cancer cells to endothelial cells leads to VE-cadherin tyrosine phosphorylation, dissociation of β-catenin from the VE-cadherin complex and the formation of gaps between endothelial cells [75]. This phosphorylation is induced by α2β1 integrin in invasive cancer cells and is mediated by the H-Ras/Raf/MEK/ERK signaling cascade and phosphorylation of the myosin light chain [75]. Likely, the VE-cadherin and α2β1 integrin interplay between endothelial and cancer cells favor endothelial cell retraction and transendothelial migration.

3.4 Cadherin 6 and cadherin 20

CDH6 is a type II cadherin involved in the morphogenesis of the central nervous system and fetal kidney [76, 77]. Cadherin 20 is mainly expressed in brain and fat tissue. Both cadherins share a high homology, including the RGD flanking sequences. Currently, no data are available about the involvement of CDH20 in cancer progression. Similar to other cadherins, CDH6 localizes to the basolateral membrane of epithelial cells and mediates calcium-dependent cell-cell adhesion [14]. It has been implicated in kidney carcinoma [52, 78, 79], ovarian carcinoma [80, 81], thyroid cancers [82, 83], cholangiocarcinoma [84], hepatocellular and small cell lung carcinoma [85], sometimes as pro-metastatic protein and sometimes as suppressor (**Table 1**). Similar to CDH17 and VE-cadherin, CDH6 seems to be strongly expressed in aggressive thyroid carcinomas [86] and nasopharyngeal carcinoma [87]. In thyroid cancer, CDH6 is under the control of the transcription factor RUNX2 and is induced by TGFβ [88], promoting EMT and cancer metastasis by restraining autophagy [89]. Proteins interact with the autophagic machinery through a short linear motif named LC3-interacting region (LIR) domain [90]. Gugnoni *et al.* demonstrated the capacity of CDH6, which contains 4 potential LIR domains, to interact with the autophagic machinery and to regulate mitochondrial dynamics. In addition, they observed an increase of CDH16 expression after CDH6 silencing, confirming the inverse correlation that exists between the expression of both kidney cadherins in thyroid carcinoma cells. Recently, mRNA expression datasets from The Cancer Genome Atlas [91] and Gene Tissue Expression [92] confirmed that the CDH6 gene is frequently expressed in ovarian serous carcinoma, renal clear cell carcinoma and renal papillary carcinoma [93]. Moreover, the discovery and optimization of a CDH6-targeting antibody-drug conjugate for the treatment of ovarian patient-derived xenografts has been reported [93].

CDH6 is also expressed in platelets. Platelet aggregation is required for thrombus formation. Integrin $\alpha_{IIb}\beta_3$ undergoes conformational change and binds fibrinogen for cross-linking

platelets and cause platelet aggregation. In addition to $\alpha_{IIb}\beta_3$, platelets also contain much lower amounts of αvβ3, α2β1, α5β1 and α6β1 integrins, which mediate other platelet functions [94]. Recently, Dunne *et al*. described a functional role for CDH6 in platelet aggregation and thrombus formation [95]. This function was mediated by CDH6 binding to, and activation of, $\alpha_{IIb}\beta_3$ integrin through the RGD motif. This binding was inhibited by specific antibodies to CDH6 or $\alpha_{IIb}\beta_3$ integrin or by the RGDS peptide. Notably, in the same study, the authors described a 60% adhesion of platelets to recombinant VE-cadherin [95]. However, the role of α2β1 integrin was not investigated in this report, as it does not bind fibrinogen. Given the contribution of platelets to tumor metastasis [96], it would be interesting to investigate whether α2β1 integrin plays a role as receptor for CDH6, either in platelets, endothelial cells or cancer cells. Alternatively, CDH6 might interact preferentially with "canonical" RGD receptor integrins in metastatic cells, as occurs with $\alpha_{IIb}\beta_3$ integrin in platelets. Indeed, some cancer cells seem to express $\alpha_{IIb}\beta_3$ integrin [97, 98]. This different binding to integrins might be explained by the different RGD flanking sequences present in CDH6. The CDH6 interaction network in cancer cells, and the role of its RGD motif in metastasis (if any), needs to be clarified.

4. Effect of flanking sequences in RGD binding: differences between human and mouse RGD cadherins

Cadherin RGD sequence alignment showed the highest similarity between flanking residues of CDH17 (YSL.RGD) and VE-cadherin (Domain 3 RGD) (Y.SIL.RGD) human sequences [6] (**Figure 1**). There is also a high homology between the human CDH6 (DQD.RGD.GSL) and human CDH20 (DMD.RGD.GSI) flanking sequences, which are quite different from CDH17 and VE-cadherin and contain charged residues at positions –1 and –3 from the RGD site. Flanking sequences for CDH16 (RAI.RGD.TEG) differ from the rest. For α2β1 integrin activation, incubation with 9-mer RGD peptides from CDH17, VE-cadherin, CDH6 and CDH20 cause β1 integrin activation to different extents in all tested cancer cell lines (colorectal, breast and

melanoma) [99]. The only exception is the CDH16 RGD sequence, which did not induce any integrin activation. In any case, peptide activation results cannot necessarily be extrapolated to the full proteins, for which other allosteric factors might play a role.

Many snake venoms contain RGD motifs that are potent integrin antagonists, inhibiting platelet aggregation [100]. These toxins present some specific amino acid residues around the RGD motif, with RGD.W, A.RGD.D and RA.RGD.NP being the most common motifs in snake venom [100]. Depending on the type of flanking amino acids, venoms are very effective in selectively inhibiting the interactions of fibrinogen (and perhaps CDH6) with $\alpha_{IIb}\beta_3$ integrin and vitronectin, or fibronectin with αvβ3 and α5β1. These flanking sequences differ completely from the RGD sequences in cadherins. Snake venom RGD motifs have demonstrated that manipulation of the flanking sequences seems to be a universal mechanism for blocking different ligands and for modulating the affinity of binding to different integrins.

Cadherin RGD motifs are not equally preserved in all mammals. Whereas CDH17 sequences in primates contain RGD motifs, those in rodents and other small mammals do not [6]. A similar situation occurs for VE-cadherin, which contains RGD motifs within different domains (e.g. 1, 2 or 3) in many mammals and some birds, but not in rodents or dogs. Indeed, the VE-cadherin sequence in most primates contains two RGD domains. It is unclear whether this duplication of the RGD motif provides some evolutionary advantage to primates related with the average life span, as rodents have shorter lives than other mammals. Remarkably, CDH6 RGD motif is the only one conserved in human, mouse and almost any investigated species, suggesting that it has a critical function that must remain well preserved among species. This critical function might be related with platelet aggregation and blood coagulation. The lack of RGD cadherins in mouse (except CDH6) raises the question about the adequacy of using mouse models for human cancer metastasis in some tumors, such as colorectal or breast cancer. Differences in

RGD composition might also explain some conflicting results between human and mouse metastatic models.

5. Integrins in cancer: colonization and late metastasis

Integrins are transmembrane receptors that form cell-cell and cell-matrix adhesions [101]. Mammalian genomes contain 18 α subunits and 8 β subunit genes that enable up to 24 different αβ combinations at the protein level. Focusing on solid tumors, these integrin pairs are classified into three groups: β1-containing integrins, αv-containing integrins (αvβ3, αvβ5, αvβ6 and αvβ8) and α6β4 integrin [101]. Alternatively, they have been classified according to their receptors and putative ligand partners, such as RGD, collagen, laminin and leukocyte-specific receptors (which bind to LDV motifs). This classification has had a large impact on subsequent studies of integrins and their role in cancer metastasis. For instance, α2β1 integrin has been classified as a collagen receptor, but not as RGD receptor.

Integrins are not classic signaling receptors, as they do not possess enzymatic activity [102]. Integrin signaling depends on the allosteric behavior of the receptors and their ability to concentrate into adhesion zones and to recruit new components to the integrin-based cell adhesion [103]. Integrins sense physiological and pathological events triggering different cellular responses, connecting the inside and outside of a cell for bidirectional signaling to control cell adhesion, migration, proliferation survival and differentiation [104]. After binding a specific ligand, some integrin subunits undergo major conformational changes, from an inactive low avidity state to a high avidity state [105]. Most integrins are not specific for single ligands; rather, each integrin binds several ligands, and some ligands are recognized by multiple integrins. Extracellular matrix proteins (such as collagens, fibronectin, vitronectin and laminins) are considered as major ligands of integrins. Integrin activation triggers a canonical signaling cascade through different molecules (e.g., FAK, Src and Ras), which in turn activates ERK and MAPK through BRAF. Integrins cluster to form focal adhesions, which are implicated in

cytoskeletal reorganization [106] and cell cycle progression [107]. In summary, integrin signaling promotes and facilitates the different steps also involved in metastatic progression. However, the function of integrins in specific colonization of distant organs by cancer cells still requires further clarification.

Regarding the RGD motif, the history of studying RGDs started in the mid-80s with the seminal publications of Pierschbacher and Ruoslahti [108], in which they identified the tetrapeptide RGDS in fibronectin as a critical site for regulating cell attachment. One year later, the same group described the heterodimeric receptor for fibronectin, which turned out to be α5β1 integrin [109]. About one-third of 24 integrin heterodimers were classified as RGD receptors, according to Hynes' classification [101], although about half of the integrin receptors have been shown to bind to RGD sites in different proteins [110]. A wide diversity in promiscuous binding to RGD motifs has been observed for the different integrins, as additional parameters, such as the conformation and presentation of the RGD motif within a structural scaffold and some allosteric effects of the RGD sequence, are critical for the binding of RGD-binding integrins. Differences in the individual sizes and shapes of the RGD loops in different proteins are also vital for the affinity and integrin selectivity of the RGD sites. Moreover, how individual amino acid residues immediately flanking the RGD sequence contribute to integrin affinity and specificity is far from obvious, although it is highly relevant for the final binding, and there are no predictive rules about their effects on different integrins. Much more structural work needs to be done in this regard.

RGD motifs have been mainly implicated in cellular integrin interactions with extracellular matrix proteins and proteins involved in hemostatic control. Multiple drugs based on RGD peptides and peptidomimetics have been trialed as antagonists of integrin activation and for specific inhibition of integrin attachment to extracellular matrix proteins [111] or for promoting increased vascular and tissue permeability [112]. One of these, a cyclic RGD peptide

(Cilengitide™) designed to block the ligand binding site of αvβ3 and αvβ5 integrins, reached clinical trials for glioblastoma [113] but did not lead to significant improvements in disease outcome [114]. In terms of cancer therapy, none of these has shown clear effectiveness. The lack of success of RGD peptidomimetics in cancer therapy has provoked a drastic loss of interest in RGD research from the therapeutic point of view in the last years. The possibility of integrin activation by RGD motifs present in other cellular plasma membrane proteins was never considered as a possibility to the best of our knowledge.

6. α2β1 integrin and type IV collagen in cancer metastasis

The α2β1 integrin (also designated VLA-2, GPIaIIa or CD49b/CD29) is an I domain–containing integrin. The (inserted) I domain is a highly conserved, extracellular, domain that mediates binding to collagens [115]. The α2β1 integrin is expressed on a variety of cell types including platelets, white blood cells, endothelial and epithelial cells and fibroblasts [116]. Elevated α2β1 integrin expression has been associated with both normal and cancer stem cells and is found on epidermal [117] and prostate stem cells [118]. In the intestine, α2β1 integrin is expressed in the stem/progenitor cell zone during normal differentiation. Overexpression of α2 integrin subunit enhances endocrine and mucous lineage commitment, suggesting a possible role for α2β1 as a regulator of cell fate in human pluripotent colorectal cancer cells [119, 120].

Pioneer studies of α2β1 integrin were related to its expression in human platelets and its role in homeostasis, thrombosis, epithelial differentiation, wound healing, angiogenesis and inflammation (see [121, 122] for reviews). α2β1 integrin was identified as the only collagen-binding integrin in platelets and was found to be crucial for deposition on collagens exposed in damaged arterial walls, which led to its classification as a collagen receptor [123]. Accordingly, elevated expression levels of α2β1 integrin have been associated with myocardial infarction and stroke [124]. Although collagen molecules contain RGD motifs, the RGD function in

collagen recognition by α2β1 integrin is unclear and has given some conflicting results [125]. For instance, α2β1 integrin was reported to be able to interact with a cyclic RGD peptide C*GRGDSPC* [125]. However, α2β1 integrin has been always classified as a high affinity receptor for type I collagen via the GFOGER (O= hydroxyproline) collagen motif [126] even though it also recognizes the network-forming collagen IV [127], the beaded filament forming collagen VI and the transmembrane collagen XII when in an active high-affinity conformation [128]. Type IV collagen (but not type VI or type XII) contains a GFPGER motif, although the presence of a hydroxylated proline in that motif has not been investigated. α2β1 integrin also works as a receptor for α1 and α2 laminins (through their N-terminal globular domains) [129], other extracellular matrix proteins (such as tenascin and thrombospondin) and proteoglycans (e.g., perlecan and decorin) (**Figure 1**). Furthermore, some infectious viruses and other microorganisms use α2β1 integrin for attachment for entrance into the cell (see [121] for a review). α2β1 integrin exists in at least two conformations, an active and an inactive one; these distinct conformations have also been observed for other integrins, such as αIIbβ3 and αvβ3 [130]. Activation of α2β1 might be induced by different molecules, including divalent cations and activating antibodies, as well as by phosphorylation by different intracellular kinases. As a consequence of this activation, α2β1 integrin binds its ligand more avidly and triggers various cellular responses [110].

Due to its exclusion from the RGD-receptor integrin family classification, characterization of α2β1 integrin has been quite neglected within the vast cancer metastasis research literature for many years. RGD receptor integrins, such as αvβ3, α4β1 and α5β1, have been preferentially associated with cancer metastasis and its therapy rather than α2β1 (see [104, 131] for reviews). On top of that, results obtained from the MMTV-neo mouse models of breast cancer suggesting that α2β1 might be a tumor suppressor [121, 132, 133] had a big impact in the field. Nonetheless, in that model, no differences were observed in the lung colonization step between wild-type and α2-null cells in wild-type animals that developed

metastasis. Moreover, human data were obtained from “in silico” analyses of transcriptomic databases [132]. However, in the last years, growing evidence underscores the critical relevance of α2β1 integrin as a key regulator of cancer metastasis in human cancer cells [6, 7, 134, 135]. A key role for α2β1 integrin has been well established in human melanoma, breast, rhabdomyosarcoma, gastric, prostate and colon cancer for lung and liver metastasis [7, 45, 136-140]. α2β1 integrin plays a major role in regulating cell migration, proliferation and survival [141]. On the other hand, studies have also established that the β1 integrin subunit plays an important role in the extravasation of metastatic cells [142], and β1-containing integrins are key for the proliferation of metastatic cells in the lung, whereas αv-containing integrins do not play a significant role [143].

Collagen is a critical component of the extracellular matrix (ECM) and the tumor microenvironment [144, 145]. Cell attachment to collagen is mainly mediated by the integrins α1β1, α2β1, α10β1 and α11β1 [101]. Integrin-mediated attachment to collagen in the ECM is a critical step for determining the capacity of cancer cells to invade locally and, ultimately, to form distant metastases. Interestingly, although α2β1 shows higher affinity for type I collagen *in vitro*, it is expressed on epithelial cells that are in close contact with a type IV collagen–rich basement *in vivo* [146]. Type IV collagen is found primarily in the basement membrane (BM) of epithelial tissues, including liver vasculature. In general, BM separates the epithelium from the stroma of any given tissue [147]. BMs are usually found in a basolateral position to epithelial cells, where cadherin expression usually occurs. The molecular composition of BMs is unique for each tissue, and BM is almost absent in lymph nodes and other lymphatic tissues in which the presence of a critical mass of tumor cells in the subcapsular sinuses is likely to promote metastasis at the regional level. This obviates the need for metastasizing cells to acquire properties for extravasation, increasing the probabilities of metastasis [148]. These differences might explain the molecular differences observed in cells obtained from lymph node or liver metastasis (i.e., SW620 and KM12SM cells in colorectal cancer [149]).

The non-fibrillar collagens, such as types IV and VI, provide a flexible support for endothelial and epithelial cell attachment and development, which may explain the preferential binding of α2β1 integrin to type IV collagen in liver metastasis. Accordingly, type IV collagen–derived signals are critical for liver metastasis in diverse tumor types [150]. Indeed, it has been reported that α2 integrin subunit mediates type IV collagen–dependent activation of focal adhesion kinase (FAK) in selective metastasis to the liver [139]. Moreover, type IV collagen induces an increase of α2β1 integrin plasma membrane expression in Caco-2 cancer cells [151], suggesting some sort of feedback loop between the integrin and collagen IV. In any case, α2β1 integrin is also involved in bone and lung metastasis of prostate and breast cancers due to its increased binding to type I collagen [152, 153]. These results suggest that α2β1 integrin binds different collagen types depending on the cancer type and the colonization organ.

7. RGD cadherin–α2β1 integrin interactions in cancer progression

Although an increased expression of α2β1 integrin has been shown in multiple metastatic cancer cells, its specific mechanism of action in these cancer cells had been unclear until recently. A simultaneous increased expression of CDH17 and the α2 integrin subunit, but an unchanged level of expression of the β1 integrin subunit, was reported for metastatic colorectal cancer cells, suggesting that these two proteins need to be increased to promote metastasis [44]. Proteomic analysis of the CDH17 interactome showed that α2, β1, α6, β4 and αv were the most abundant integrin subunits in metastatic KM12SM colorectal cancer cells [45], although α1 and α3 were also detected by flow cytometry in KM12SM cells, but not α4 and α5 [99]. No role was observed for the α6β4 integrin or the α1, α3 or αv subunits in the prometastatic properties of CDH17 in colorectal cancer cells. Using co-immunoprecipitation experiments and other techniques, an interaction between the RGD motif of CDH17 and α2β1 integrin was demonstrated to cause β1 integrin activation and to trigger the signaling pathway

and phosphorylation of FAK, Ras, ERK1/2 and cyclin D1 (**Figure 2**). CDH17-mediated activation of α2β1 integrin increased cell adhesion to type IV collagen and proliferation in metastatic colorectal cancer cells [6, 45]. Furthermore, after *in vivo* inoculation of Swiss nude mice, tumor cells expressing CDH17 containing a mutant RAD motif showed a considerable suppression of tumor growth and liver colonization.

A potential generalization of this phenomenon to other types of cancer and VE-cadherin was investigated in pancreatic cancer, melanoma and breast cancer with positive results. Pancreatic cancer cell lines also express CDH17 and respond to α2β1 integrin activation by RGD peptides. Melanoma and breast cancer cell lines show an increased expression of VE-cadherin [7], which causes the activation of α2β1 integrin for increasing cell adhesion to Matrigel and type I collagen, invasion and proliferation of metastatic cells through their RGD motifs (**Figure 2**). VE-cadherin RGD peptides promote lung colonization in melanoma and breast cancer [7]. Therefore, in human metastatic cancer cells, VE-cadherin uses a mechanism based on the integrin pathway activation that differs from that proposed for mouse fibroblastoid mammary cancer cells, which was based on the activation of the TGFβ pathway via Smad2 phosphorylation [67]. In summary, CDH17 and VE-cadherin bind and activate α2β1 integrin to enhance its binding to type I and/or type IV collagen, facilitating cancer metastasis in different organs. This model modifies the classical notion that α2β1 integrin binds collagens in a RGD- and conformation-independent way [154, 155].

Still, there are some differences between CDH17 and VE-cadherin regarding cell signaling beyond cell type expression specificity. Integrin activation mediated by CDH17 promotes adhesion and proliferation in colorectal cancer [45], while VE-cadherin also regulates invasion in melanoma and breast cancer cells (**Figure 2**). This could be explained by the fact that VE-cadherin contains a functional cytoplasmic domain for the interaction with catenins [54], but the CDH17 small cytoplasmic domain is not adequate for intracellular signaling. In cancer cells,

VE-cadherin maintains the cytoskeleton binding capacity (actin-binding) for SRC or FAK activation without interacting with β-catenin. In contrast, β-catenin is present in the CDH17 interactome [45]. Interestingly, RGD motifs in VE-cadherin are not required for cadherin-cadherin homotypic interactions in cancer cells [7]. Therefore, the dissociation of the homotypic cell-cell interactions from the integrin signaling might avoid interference with vascular stability after VE-cadherin targeting with RGD-specific antibodies.

The function of CDH6 in cancer metastatic cells (thyroid, ovarian and endometrial cancer, among others) seems to be more complex and requires further investigation, as the only published report for the CDH6 RGD describes its binding to αIIbβ3 integrin in platelets (**Figure 1**). Therefore, since its RGD flanking sequences are different from those of CDH17 and VE-cadherin, CDH6 might bind and activate some integrins classified as canonical RGD receptors (i.e. αIIbβ3 or αvβ3) in those tumors. Although peptides containing the RGD motif from CDH6 are able to activate α2β1 integrin in cancer cells lacking αIIbβ3 integrin, further research on the interactions of CDH6 RGD with αIIbβ3, αvβ3 or α2β1 in these types of cancer is required. In perspective, although a correlation between RGD cadherin expression and poor prognosis have been described in several cancer types, many other cancers remain to be tested.

8. Integrins and RGD cadherins as therapeutic targets

Over the last decades, there has been a remarkable interest in the therapeutic targeting of integrins due to their multiple functions in cancer metastasis and angiogenesis. In addition, integrins are used by cancer cells in their evasive mechanisms for drug resistance. For instance, integrin β1 has been involved in HER2-overexpressing breast cancer as a driver of resistance to different drugs (lapatinib and trastuzumab) [156]. In lung cancer cells, erlotinib resistance is associated to an increase of α2, α5 and β1 subunit integrins [157]. Moreover, an α2β1 integrin–inhibited apoptosis is induced by paclitaxel and vincristine in breast cancer [158] and by 5-fluorouracil in pancreatic cancer [159]. Their implication in the maintenance and

promotion of cancer stem cells is a further contribution of integrins to relapse and chemoresistance [131]. Integrin-based antiangiogenic therapies have mainly focused on αvβ3 integrin, a classic RGD receptor [160]. The increased expression of αvβ3 promotes metastatic properties and invasion traits. αvβ3 integrin is overexpressed in different tumor types, in which it has been associated with metastasis and poor prognosis [161-163]. Inhibition of αvβ3 and αvβ5 integrins prevents angiogenesis and vascular tube formation in animal models (see [164] for a review). Various attempts at targeting αvβ3 integrin in tumors using different types of RGD peptides and peptidomimetics as antagonists have had limited success, as mentioned previously for cyclic RGD peptide (Cilengitide™) [114]. Abciximab is a chimeric mouse-human monoclonal antibody specific for αIIbβ3 integrin that also binds αvβ3. Abciximab is used to inhibit platelet aggregation by steric blocking of ligand binding [165]. No applications in oncology have been described. Different αvβ3-specific monoclonal antibodies have been tested in several clinical trials but have not produced clear objective disease responses or had a significant impact in overall survival [164].

α2β1 integrin has been targeted using blocking antibodies against the α2 integrin subunit, by for instance antibody GRB-500, which is currently in clinical trials for multiple sclerosis and ulcerative colitis [134], or antibody 4C3, which blocks the binding of α2 integrin to type I collagen and was shown to inhibit breast carcinoma bone metastasis in mouse models [166]. Furthermore, a sulfonamide derivative E7820 that inhibits α2 expression has demonstrated inhibitory activity in colorectal cancer cell lines and is currently in phase II clinical trials [167]. Targeting integrin α2 is considered safe, as α2 integrin–null mice are viable and fertile, and α2 integrin–deficient patients present only mild bleeding diatheses [166, 168]. For the integrin β1 subunit, volociximab (M-200), a humanized monoclonal antibody that targets α5β1 integrin, is currently in clinical trials for solid tumors [169].

Regarding RGD cadherins, recognition and activation of integrins by RGD cadherins represents not only a novel ligand for integrins but also an important function for targeted therapy, including overcoming drug resistance. As suggested, blocking the ligand could be more effective than blocking the receptor [170], and RGD cadherins seem to be critical ligands for metastasis progression. CDH17 and VE-cadherin silencing using siRNAs reduced tumor growth and metastasis [6, 7, 45]. Recently, synthetic peptides containing the CDH17 RGD motif and their flanking sequences elicited highly specific and selective monoclonal antibodies that inhibited β1 integrin activation and showed anti-metastatic activity in different cancer cell types expressing CDH17 and VE-cadherin (**Figure 3**) [92]. In contrast, antibodies against full-length CDH17 were ineffective [99]. Treatment of colorectal, pancreatic, breast and melanoma cancer cells with RGD-specific monoclonal antibodies inhibits signaling mediated by FAK, JNK, ERK, SRC and/or AKT to different extents depending on the cell line and the cancer type. As a general rule, proliferation-related pathways are always inhibited, whereas adhesion and invasion are cell-dependent. These RGD-specific monoclonal antibodies induce a significant increase in mouse survival after intravenous and intrasplenic injection of highly metastatic cells from melanoma and colorectal cancer, causing lung and liver metastasis, respectively, even when antibody treatment starts after cancer cell homing in the target organ [99]. The value of these antibodies for other cancer metastases expressing CDH17 and VE-cadherin (i.e. breast and pancreas), as well as their effect on already implanted metastasis, remains to be tested. Recently, treatment of ovarian cancer with a drug-conjugated CDH6-specific antibody provided a therapeutic alternative to this disease [93], but the RGD motif was not mentioned or investigated. We might consider that these RGD-specific antibodies could be applied even if the activated integrin is not α2β1 integrin, as might be the case for CDH6, as they recognize the RGD cadherin sequence, independently of the integrin sequence. In any case, the selectivity conferred by the different cadherin RGD flanking sequences might avoid unspecific

binding of these monoclonal antibodies to the RGD motifs in the ECM proteins (such as fibronectin and collagen) and other proteins.

9. Conclusions

In this review, we aimed to provide an overview of recent data that places RGD cadherins and α2β1 integrin in the spotlight of metastatic colonization in different solid tumors. Multiple sources of evidence support the multifunctional role of these proteins in cell biology and cancer progression. Such multifunctional activities are possible thanks to the capacity of CDH17 and VE-cadherin to bind to and activate α2β1 integrin. Cadherin RGD–specific monoclonal antibodies have demonstrated an extraordinary efficiency in blocking β1 integrin activation and protecting mice from liver and lung metastasis arising from colorectal cancer and melanoma, respectively. This therapy would be only effective when both molecules—RGD cadherins and integrins—are simultaneously overexpressed in the cancer cells. Moreover, these new findings about RGD cadherins properties may resolve the conflicting reports about the α2β1 integrin involvement in cancer metastasis and its ability to bind collagen I and IV with different affinities in distinct circumstances.

We hope this review foster furthers research on this family of proteins. There are many important open questions that require further clarification, including those in this (non-exhaustive) list: 1) Mechanisms for overexpression of α2 integrin in cancer intestinal cells and other tumors remain largely unexplored; 2) Given the low expression of CDH17 and α2β1 integrin in poorly differentiated tumors, the relationship between CDH17/α2β1 integrin expression and tumor differentiation requires further studies; 3) The structural basis of cadherin RGD recognition by α2β1 integrin, and its affinity increase for type IV collagen, have to be determined; 4) The capacity of the RGD-specific antibodies to impact already established metastasis, as well as its effect on other types of metastasis (e.g., peritoneal and bone) requires further research; 5) The transcription factors that trigger the overexpression of RGD

cadherins, and in particular VE-cadherin and CDH6, in metastatic cells remain to be identified; 6) The CDH6 RGD-mediated integrin activation capacity in thyroid, ovarian and other metastatic cancer cells needs to be clarified; and 7) Future studies should confirm the value of RGD cadherins as markers of metastasis and therapeutic targets in multiple types of cancer. It seems likely that efforts to elucidate the crosstalk between RGD cadherins, integrins and the extracellular matrix will lead to fruitful results for a better understanding of cancer metastasis biology.

Financial support

This research was supported by grants BIO2015-66489-R from the MINECO and Foundation Ramón Areces to J.I.C.

Conflict of interest

R.A.B. and J.I.C. are inventors of a related patent application held/submitted by the Spanish National Research Council. J.I.C. has stock ownership at Protein Alternatives SL.

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Table 1. RGD cadherins expression and clinical associations in cancer

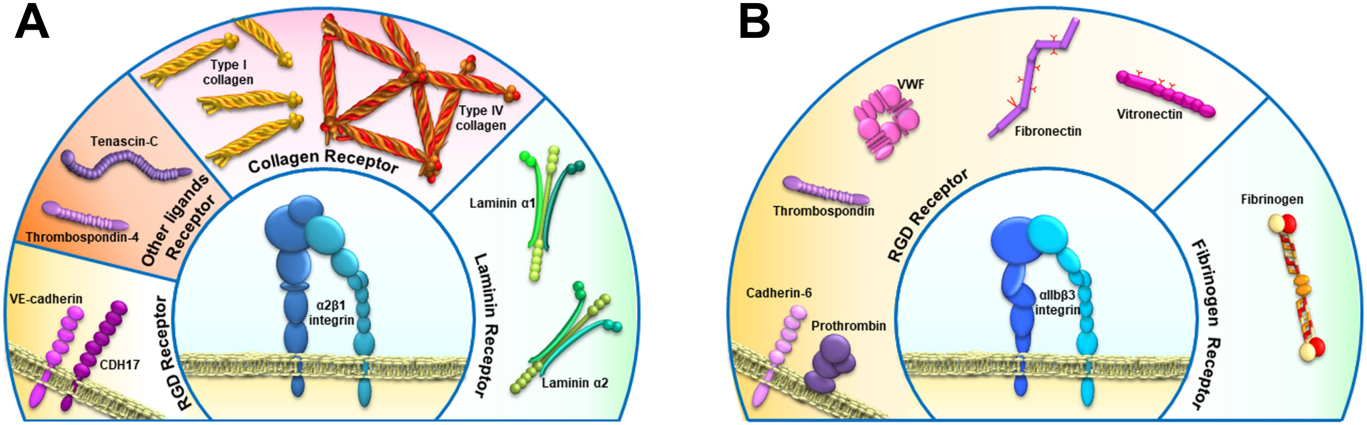
RGD cadherin	Cancer type expression	Correlation with poor survival or tumor stage
Cadherin-5	Acute lymphoblastic leukemia (70) Breast cancer (67, 71) Ewing sarcoma (66) Gastric cancer (71) Glioblastoma (63) Lung cancer (61, 68) Melanoma (69) Ovarian cancer (62) Uveal melanoma (59, 60)	Breast cancer (72, 73) Gastric Cancer (71)
Cadherin-6	Cholangiocarcinoma (84) Hepatocarcinoma (85) Nasopharyngeal carcinoma (87) Ovarian cancer (80, 81, 93) Papillary thyroid carcinoma (82, 83, 88, 89) Renal cell carcinoma (52, 78, 79, 85, 93) Small cell lung carcinoma (85)	Renal cell carcinoma (79)
Cadherin-17	Colorectal cancer (26, 38, 42, 43, 45) Gastric cancer (34, 35, 36) Hepatocarcinoma (32) Neuroendocrine tumors (40, 41) Pancreatic cancer (37, 38, 39, 41)	Colorectal cancer (38, 42, 43, 45) Gastric cancer (36) Hepatocarcinoma (34)

Legends to the figures

Figure 1. Ligands of α2β1 and αIIbβ3 integrins and RGD motifs in cadherins. (A) α2β1 integrin recognizes GFOGER motif in collagens, but also can bind RGD motifs present in cadherins and other proteins. In addition, this integrin can bind to N-terminal globular domains of α-chain of laminins. (B) αIIbβ3 integrin recognizes RGD motifs in a variety of proteins. It also binds to the sequence HHLGGGAKQAGDV in the γ-chain of fibrinogen. Flanking sequences for the RGD motifs in cadherins are represented within blue boxes.

Figure 2. RGD cadherins promote metastatic colonization. The RGD motifs present in VE-cadherin on melanoma and breast cancer cells (*left*) and CDH17 on colon and pancreatic cancer cells (*right*) interact with α2β1 integrin increasing its affinity for ligands in the extracellular matrix and, consequently, their metastatic colonization capacity in lung and liver. An increase of proliferation and integrin-mediated cell adhesion to type I and type IV collagens was observed for VE-cadherin and CDH17, respectively. For melanoma and breast cancer, VE-cadherin also promoted migration and invasion. Different mediators (FAK, JNK, ERK, SRC, and AKT) are used in each process.

Figure 3. Anti-cadherin RGD antibodies inhibit integrin activation and metastatic colonization of cancer cells. RGD cadherins bind to α2β1 integrin promoting an increase of integrin affinity for enhanced adhesion to type I and type IV collagens (*left*). Collagen adhesion triggers the activation of signaling proteins leading to the promotion of cell invasion, proliferation and, finally, metastasis in distant organs. The presence of anti-cadherin RGD antibodies (*right*) inhibits the binding of the cadherin RGD motifs to α2β1 integrin, thus blocking the adhesion and subsequent signaling by the integrin.



CDH17	YSLRGDTRG
VE-cadherin domain 2	QGLRGDSGT
VE-cadherin domain 3	SILRGDYQD

CDH6	DQDRGDGSL
CDH20	DMDRGDGSI

Figure 1

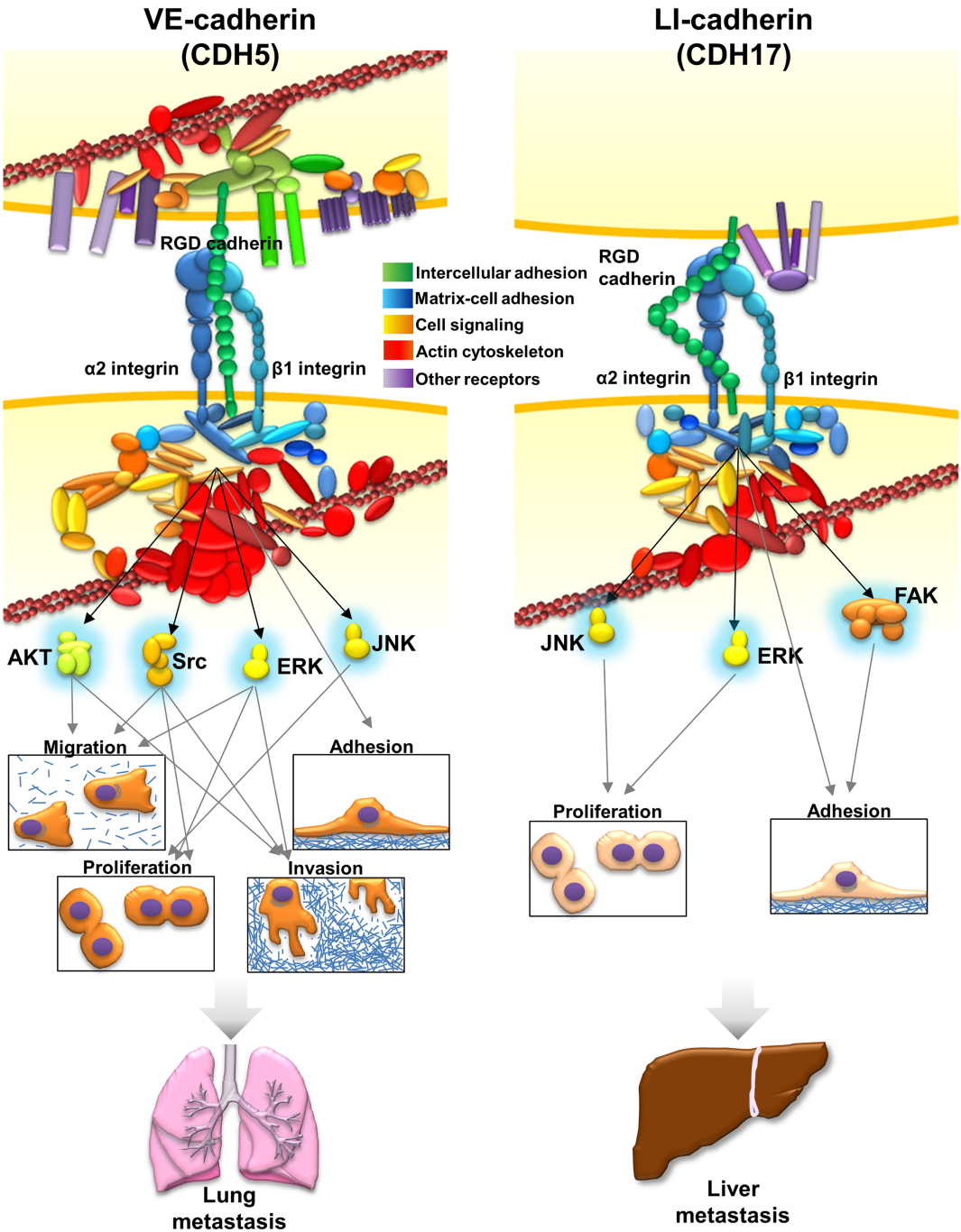

VE-cadherin
(CDH5)
LI-cadherin
(CDH17)
RGD cadherin
RGD
cadherin
Intercellular adhesion
Matrix-cell adhesion
Cell signaling
Actin cytoskeleton
Other receptors
α2 integrin
β1 integrin
α2 integrin
β1 integrin
AKT
Src
ERK
JNK
JNK
ERK
FAK
Migration
Adhesion
Proliferation
Invasion
Proliferation
Adhesion
Lung
metastasis
Liver
metastasis

Figure 2

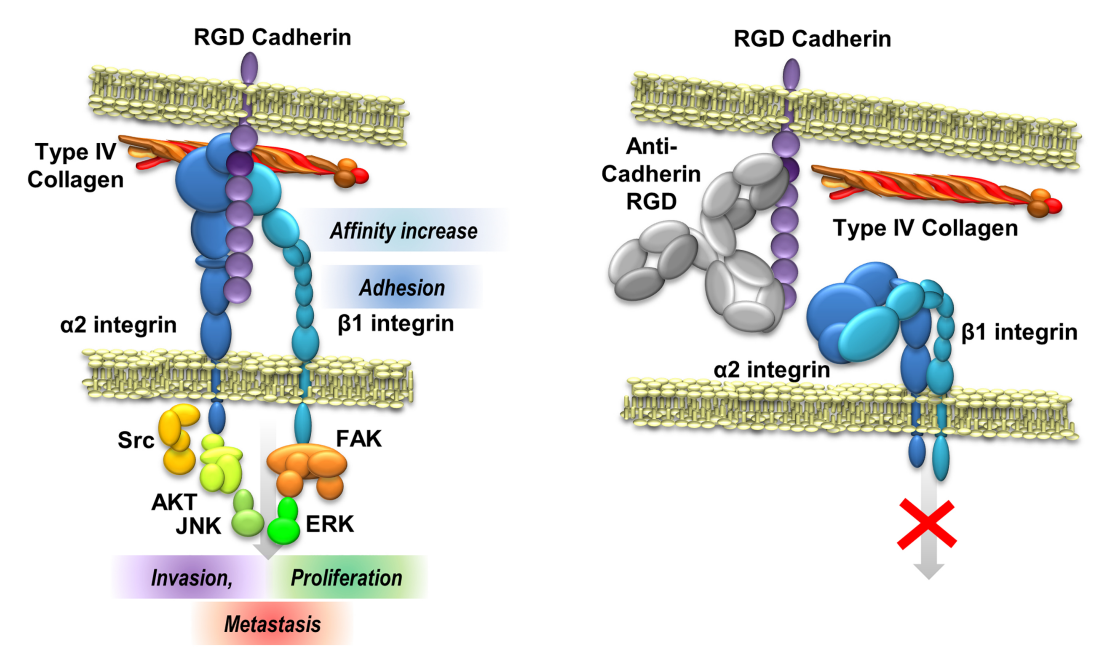

RGD Cadherin
Type IV Collagen
Affinity increase
Adhesion
α2 integrin
β1 integrin
Src
FAK
AKT
JNK
ERK
Invasion,
Proliferation
Metastasis
RGD Cadherin
Anti-Cadherin RGD
Type IV Collagen
β1 integrin
α2 integrin

Figure 3