REVIEW

Dynamic interplay between adhesion surfaces in carcinomas: Cell-cell and cell-matrix crosstalk

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Abstract

Cell-cell and cell-matrix signaling and communication between adhesion sites involve mechanisms which are required for cellular functions during normal development and homeostasis; however these cellular functions and mechanisms are often deregulated in cancer. Aberrant signaling at cell-cell and cell-matrix adhesion sites often involves downstream mediators including Rho GTPases and tyrosine kinases. This review discusses these molecules as putative mediators of cellular crosstalk between cell-cell and cell-matrix adhesion sites, in addition to their attractiveness as therapeutic targets in cancer. Interestingly, inter-junctional crosstalk mechanisms are frequently typified by the way in which bacterial and viral pathogens opportunistically infect or intoxicate mammalian cells. This review therefore also discusses the concept of learning from pathogen-host interaction studies to better understand coordinated communication between cell-cell and cell-matrix adhesion sites, in addition to highlighting the potential therapeutic usefulness of exploiting pathogens or their products to tap into inter-junctional crosstalk. Taken together, we feel that increased knowledge around mechanisms of cell-cell and cell-matrix adhesion site crosstalk and consequently a greater understanding of their therapeutic targeting offers a unique opportunity to contribute to the emerging molecular revolution in cancer biology.

Key words: Cell-cell; Cell-matrix; Adhesion; Cancer; Crosstalk; Pathogens; Epithelial; Barrier function; Tight junction; Cell migration; Apical junctional complex; Adherens junction; Adhesion molecules; Extracellular matrix; Tyrosine kinases; GTPases; Rho

Core tip: Deregulation of cell-cell and cell-matrix signaling makes well-established contributions to key elements of cancer initiation and progression. In this review we discuss mechanisms of crosstalk between these spatially-distinct adhesion sites in epithelial cells, with a view to understanding their therapeutic targeting in epithelial tumors (carcinomas). A particular focus is placed upon Rho GTPases and tyrosine kinases as mediators of inter-junctional crosstalk, in addition to the concept of opportunistic pathogenic infection as a paradigm for inter-junctional crosstalk. Overall, this review posits that a greater understanding of cell-cell and cell-matrix adhesion crosstalk will drive novel aspects of cancer drug discovery.

INTRODUCTION

The semi-permeable plasma membrane acts as a barrier between interior and external environments of the cell. The plasma membrane forms specialised domains with distinct protein and lipid compositions crucial for many biological processes like cell adhesion, signaling, directed migration, cell division, cell fate determination and barrier function. These specialised domains contain concentration gradients of proteins differentiating the cell surface into basal, lateral and apical domains; facing respectively the extracellular matrix (ECM), adjoining cells and the outside environment (schematically represented in Figure 1).

Cell-cell interactions, functions and signaling

Cell-cell junctions form part of the lateral surface domain which segregates apical and basal plasma membrane constituents[1], and act as a physical barrier in regulating substance flow across the tissues. Throughout the developmental process of higher organisms, formation and remodeling of cell-cell junctions occurs repeatedly[2]. The main cell-cell anchorage systems are tight junctions (TJs), adherens junctions (AJs) and desmosomes, which are distinguished from one another structurally and based on molecular composition.

TJs

TJs are seen in various cell types like epithelial, vascular endothelial, mesothelial, schwann, oligodendrocytes and sertoli[3]. In mammalian cells TJs appear at the apical end of the lateral intercellular membrane, whereas in invertebrate-like insect epithelial cells their counterpart septate junctions are located in the basal domains. TJs also demarcate the boundary between the apical and basolateral membrane domains of a cell and serve as a semipermeable barrier to the transport of ions, solutes and water[3]. TJs are multi-protein complexes that can be subdivided into integral membrane and cytoplasmic plaque proteins. Junctional adhesion molecules (JAMs), occludin, claudins, tricellulin and marvelD3 are integral proteins that mediate cell-cell adhesion[4], while ZO-1, -2, -3 and cingulin are cytoplasmic proteins that connect membrane proteins to the cytoskeleton[5]. Occludin, tricellulin and marvelD3 contain a Marvel (MAL-related proteins for vesicle trafficking and membrane link) domain. Claudin, occludin, tricellulin and marvelD3 are tetra-spanning proteins with both N and C termini in the cytosol, and which possess two extracellular loops. JAMs belong to the immunoglobulin (Ig) superfamily and consist of two extracellular Ig domains, a single transmembrane domain and a C-terminal cytoplasmic domain containing a PDZ-interacting domain. Alterations in epithelial TJs have been reported to contribute to a variety of pathologies including inflammation and cancer, yet a complete mechanistic understanding of these phenomena remains elusive. For a more comprehensive review of this topic, the reader is directed to the following reviews[6,7].

AJs

AJs are complexes that form the initial link between neighbouring cells in a developing tissue barrier, and thereby make important contributions to embryogenesis and tissue homeostasis[8]. The core structural components of AJs are Nectin and Cadherin family cell adhesion molecules, which are linked to the actin cytoskeleton through their binding proteins afadin and catenins[9,10]. Cadherin extracellular domains form calcium-dependent homophilic interactions between neighboring cells[11], while their cytoplasmic domains interact with three distinct known catenins (α, β, γ)[10]. Nectins (1-4) are calcium-independent adhesion proteins with three IgG like loops in their extracellular domains and a cytoplasmic domain containing a C-terminal PDZ binding motif[10,12].

Desmosomes

Desmosomes are intercellular junctions that link intermediate filaments (IFs) to sites of intercellular adhesion, facilitating the formation of supracellular scaffolding that distributes mechanical forces throughout a tissue[13]. They are observed particularly in tissue types that experience mechanical stress, such as the intestinal mucosa, gallbladder, uterus and oviduct, liver, pancreas, stomach, salivary and thyroid glands and the epithelial cells of the nephron, but are most abundant in the skin and myocardium[14,15]. The components of desmosomes come from three gene families: Desmosomal cadherins (desmogleins and desmocollins), the armadillo family of nuclear and junctional proteins (plakoglobin and plakophilin 1-3) and finally the plakins (desmoplakin,
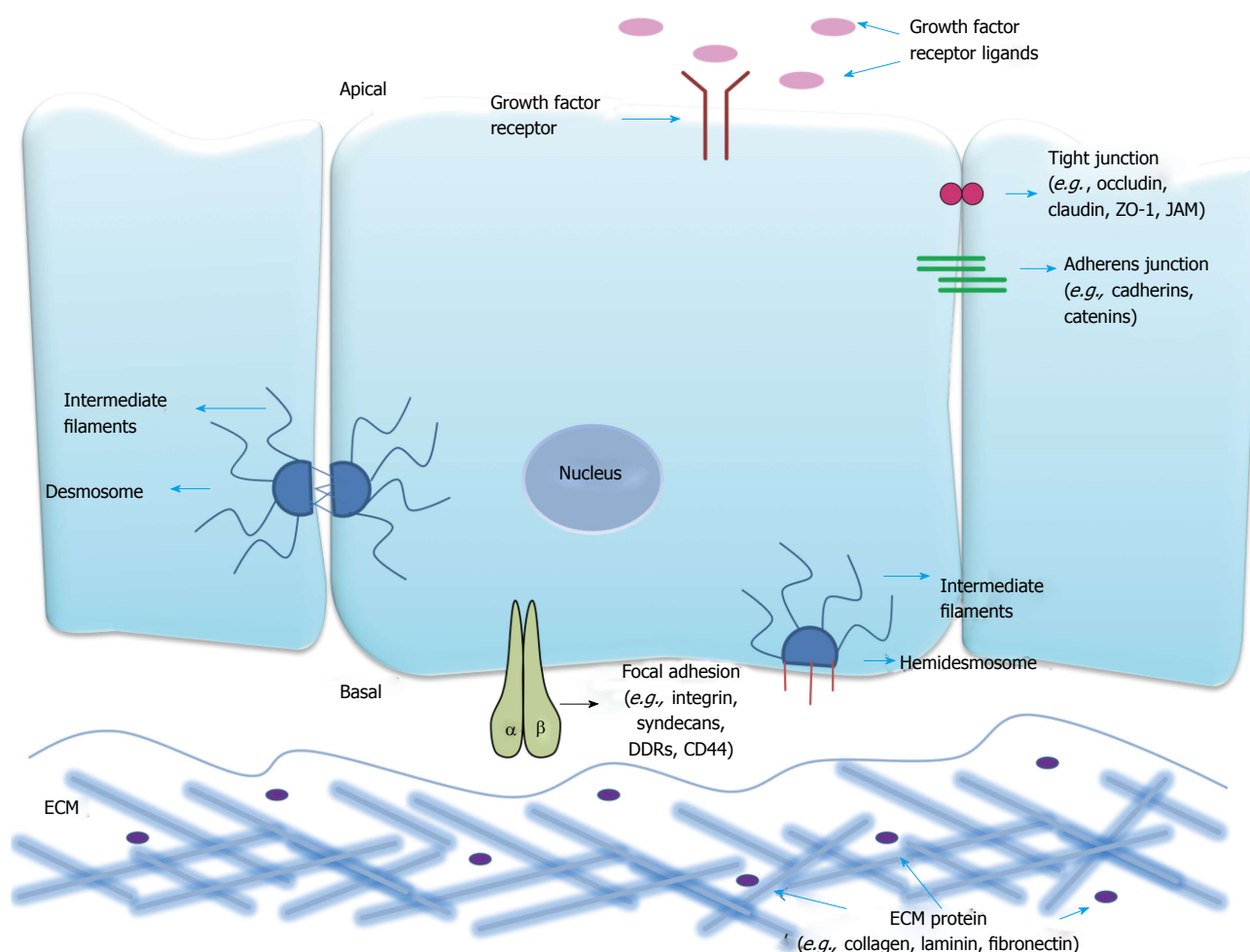
Figure 1 Epithelial cell-cell and cell-matrix junctions. Schematic drawing of key epithelial cell-cell and cell-matrix junctions, with representative constituent proteins listed as discussed in the manuscript text. ECM: Extracellular matrix; DDRs: Discoidin domain receptors; JAM: Junctional adhesion molecule.

plectin, envoplakin, periplakin)[16]. The cytoplasmic tails of desmosomal cadherins provide binding platforms for the armadillo family members. The plakin family members in turn link the stress-bearing IF cytoskeleton to specialized regions of the plasma membrane[13]. This interaction of IFs with desmosomes propagates the tensile strength imparted by the IF cytoskeleton across entire tissues, and is essential for tissue integrity[17].

Cell-matrix interactions, functions and signaling
Interactions between cells and the ECM are important in the overall architecture and maintenance of tissue integrity[18]. During development, these interactions play key roles in tissue morphogenesis, cellular polarisation and epithelial cell attachment[19,20]. Cellular interactions with the ECM rely upon interactions between ECM proteins, focal adhesion receptors and signaling molecules, including those of the cytoskeleton, to form multifaceted adhesion complexes. We refer interested readers to a recent review which discusses these complexes in further detail[21].

A plethora of cell-matrix proteins exist and are dynamically regulated depending on the tissue location, organisation, structure and components of the tissue microenvironment. This in turn dynamically regulates cellular responses[18]. Communication between cells and the ECM is mediated by transmembrane focal adhesion receptors including syndecans, discoidin domain receptors (DDRs), CD44 and integrins.

Syndecans are heparin sulfate proteoglycans that span the plasma membrane. Syndecans have been shown to play a role in multiple cellular processes including migration, differentiation and organisation of the ECM and cytoskeleton, features which are attributed to the presence of glycosaminoglycan chains in the extracellular domain[22].

DDRs are members of the receptor tyrosine kinase (RTK) family with collagen-specific ligands[23]. Collagen binds to DDR causing tyrosine phosphorylation and consequent activation of downstream signaling pathways. While the specific mechanisms of action of DDRs are still being elucidated, DDRs have been identified as important receptors in regulating cell polarity, adhesion, migration and invasion[24]. In addition, DDRs have been suggested as negative regulators of integrin signaling[25].

CD44 is a glycoprotein and member of the hyaluronate family of receptors. It mainly binds the ECM protein hyaluronan but can also bind other ECM proteins

including laminin, collagen and fibronectin[26]. CD44 is known to regulate cellular growth, differentiation, survival, migration and adhesion through different mechanisms including direct ligand binding, formation of co-receptors with RTKs and binding to ERM (ezrin, radixin and moesin) proteins thereby forming a link between the membrane and actin cytoskeleton[27].

Integrins are heterodimeric transmembrane receptors composed of α and β subunits that are considered the main matrix adhesion receptors mediating intracellular, cytoskeletal and ECM interactions[28]. Integrins can signal bidirectionally across the membrane, whereby intracellular signals can cause extracellular changes ("inside-out" signaling) and extracellular signaling can cause intracellular changes ("outside-in" signaling)[29]. Intracellular signaling *via* integrins is mediated through different signaling mediators including focal adhesion kinase (FAK), mitogen-activated protein kinases (MAPK) and members of the Rho-GTPase family[30]. Extracellular ligands for integrins include collagens, laminins or RGD-containing proteins[31]. Integrins regulate numerous important cellular features including migration, proliferation, survival and differentiation[32].

ECM remodelling is an important feature influencing cell to cell communication, a process which is regulated by degradation and modification of components of the ECM. Matrix metalloproteinases, ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) and serine proteinases play a major role in this process to maintain homeostasis within the ECM[33].

CELL-CELL AND CELL-MATRIX CROSSTALK

Non-RTK signaling

Signaling crosstalk is an interaction between two or more independently-initiated signaling pathways, the outcomes of which include the amplification or attenuation of the signal. In the context of crosstalk between cell-cell and cell-matrix adhesive signaling, it is intriguing to note that both sites contain not only structural proteins but also signaling effectors which fit the bill as potential mediators of crosstalk. Notably, a number of non-RTKs are localized to cell-cell and cell matrix adhesions and act as key players regulating crosstalk in the context of adhesive networks[34-36]. Furthermore, tyrosine kinase signaling is one of the most frequently deregulated signaling pathways in solid tumors, and has been well established to contribute to the initiation and progression of tumors[37].

Non-RTK proteins in conjunction with cell-cell and cell-matrix adhesion are crucial effectors of a broad range of stimuli, and mediate activation of signal transduction events regulating cell survival, morphology and migration of malignant and non-malignant cells. One of the key molecules in this respect is the non-RTK Src, activation of which has dual functions in regulating formation of cell-cell and cell-matrix adhesions. Src is

recruited and activated upon E-cadherin ligation and this provides a positive feedback loop that signals through Phosphoinositide-3 Kinase (PI-3 kinase) to promote the stability of cell-cell contacts[36]. However, constitutively active Src disrupts cell-cell contacts and alters cell morphology[38], and its presence at integrin-matrix adhesions leads to peripheral accumulation of activated myosin, leading to disruption of cell-cell junctions[39]. Recent studies have focused on Src-dependent regulation of E-cadherin and other tumor progression-related events such as epithelial to mesenchymal transition (EMT) with the development of metastasis. In pancreatic adenocarcinoma, c-Src (Src) is frequently activated and controls tumor progression[40,41]. The amount of E-cadherin protein in a cell plays an important role in tumor progression to invasive, metastatic carcinoma[41,42]. It was shown that Src downregulates E-cadherin and induces EMT, favoring metastasis in pancreatic adeno-carcinoma[41]. In breast carcinomas, complete loss of E-cadherin may be an important step in the formation of lobular carcinoma *in situ*, as a precursor of invasive lobular breast cancer[43]. In colon cancer, Src-induced deregulation of E-cadherin has been shown to require integrin signaling[44]. Another study showed how the ECM environment controls tumor growth[45]. Specifically, in pancreatic cancer cell lines with high metastatic potential, E-cadherin expression levels were normal and cells possessed functional E-cadherin/catenin complexes. When the cells were cultured on type I or III collagen, E-cadherin gene expression was repressed and E-cadherin and catenin protein concentrations were reduced. In contrast, growth on fibronectin or collagen IV had no effect on the level of E-cadherin. Overexpression of activated c-Src in pancreatic cancer cells mimicked collagen-induced E-cadherin down-regulation and altered cell migration[45]. In non-transformed mammary epithelial cells PI-3 Kinase-Rac1-c-JNK signaling has been associated with collagen I -induced cell scattering, up-regulation of N-Cadherin and consequent EMT[46]. It has been reported that other members of the Src kinase family mediate crosstalk between cell-cell and cell-matrix junctions, including the proto-oncogene c-Yes which is known to regulate epithelial tight junction formation by phosphorylation of a key tyrosine residue in occludin[47].

Further illustrating the potential importance of Src signaling in cell-cell to cell-matrix site crosstalk, the Src substrate FAK, itself a non-RTK, has also been shown to act as a downstream effector of integrin adhesion and signaling. By virtue of its binding to intracellular regions of β-integrin subunits, FAK plays a pivotal role as a signal integrator downstream of cell-ECM interactions and other receptor and non-RTKs[48]. Furthermore Src-FAK signaling promotes E-cadherin internalization during cancer progression, thus facilitating EMT and enhanced tumor cell motility[49]. In other cell types, as is the case with KM12C colon cancer cells that have retained E-cadherin, FAK can also have a negative influence on cadherin-mediated intercellular adhesion[44].

The non-RTKs Fes/Fer also regulate cell adhesion

and cytoskeletal reorganization through the modification of AJs[50]. Fer is involved in communication between cell-cell and cell-matrix junctions by shuttling between N-cadherin-containing AJs and β1-integrin focal adhesion (FA) complexes[51]; and can be activated by either cadherin or integrins[34,52,53]. Fer phosphorylates cadherin-associated cortactin and this process is involved in mediating intercellular adhesion strength[54]. In breast cancer Fer has been speculated to promote metastasis by regulating α6 and β1 integrin-dependent cell adhesion[55].

Given the fact that a number of non-RTKs mediate crosstalk between cell-cell and cell-matrix adhesion sites, any deregulation in the signaling network could have profound impacts on cell-cell and cell-matrix adhesion favoring malignancies.

RTK signaling

Several growth factor RTKs have also been reported to regulate cell-cell and cell-matrix adhesion both in cancer and normal cells. Among those, Ephrin receptors have been implicated in crosstalk with β-integrins in prostate cancer cells to strengthen adhesion to collagen type I and preferentially metastasize to collagen I -enriched bone tissue[56]. During breast cancer development, cancer cells metastasize to distant organs and interact with ECM and stroma to survive and remain dormant[57]. Another RTK which has been linked to adhesive crosstalk is the fibroblast growth factor (FGF) receptor. Specifically, estrogen-dependent breast cancer cells have been shown to be partially re-differentiated by FGF-2, which initiates upregulation of integrin α5β1 lost during malignant transformation[58]. Dual signaling by FGFR through PI3K and independently through integrin α5β1 induces activation of FAK and membrane localization and activation of the small GTPase RhoA and GRAF, a GTPase-regulator associated with FAK. This results in inactivation of RhoA, cortical rearrangement of F-actin and consequent switching of cancer cells to a dormant phenotype that promotes cancer cell survival[59]. In normal cells RhoA is essential for the assembly and function of epithelial cell-cell junctions whereas overexpression of RhoA in rat hepatoma cells induces an invasive phenotype[60]. Apart from this, FGFR signaling promotes cell adhesion in pancreatic cancer cells. N-CAM stimulates β1-integrin-mediated cell-matrix adhesion by activating FGFR signaling and could be a potential mechanism for preventing dissemination of tumor cells[61]. Activation of another growth factor receptor, that for EGF, prevents disruption of TJs in colon cancer cells. Specifically MAPK has been shown to interacts with occludin and mediates EGF-induced prevention of TJ disruption following hydrogen peroxide exposure[62]. Finally, the IGF1 receptor forms a ternary complex with E-cadherin and αv-integrins at cell-cell contacts in cultured colon cancer cells and human normal colonic mucosa. IGF1 binding to this receptor disrupts the complex and causes relocalisation of αv-integrins to focal contacts in conjunction with an increase in cell migration[63].

RTKs are known to play key roles in regulating several biological processes, and crosstalk with cell adhesion molecules is important in the context of normal development. However a large body of evidence from different laboratories suggests that such cooperation between cell-cell, cell-matrix and RTK signaling regulates cellular behaviors that are important for cancer progression.

Rho GTPases and signaling

Rho GTPases (guanosine triphosphatases) comprise a family of proteins within the Ras-like small G protein family, and include the molecules Rho, Rac, and Cdc42[64]. Rho GTPases play an important role in maintaining cell structure and polarity through their critical influence on dynamics of the actin cytoskeleton, thereby regulating cellular processes including cell adhesion and coordinating cell-cell and cell-matrix adhesion complexes[65]. Increased expression of Rho GTPases has been linked to many different cancer types including breast, lung, colorectal, testicular and prostate cancer[66-70]. Aberrant signaling of Rho GTPases has been attributed to promoting features of tumorigenesis including migration, invasion, cell survival, angiogenesis and metastasis[71]. As Rho GTPase molecules play an important role in regulating actin dynamics, cell adhesion and signaling processes, both at the cell-cell and cell-matrix level, it poses the question whether Rho GTPases mediate crosstalk between cell-cell specific and cell-matrix specific proteins and pathways, with particular reference to their involvement in cancer.

Rho GTPases are active when bound to GTP and inactive when bound to GDP, and a range of regulatory factors that dynamically influence the exchange kinetics of such reactions can themselves be signal control points or drug targets in cancer. These include the families of guanine nucleotide exchange factors which promote increased binding of GTP and therefore increase Rho GTPase activity[72]. In contrast, GTPase activating proteins inactivate GTP signaling by inducing GTP hydrolysis[72,73]. The switch between membranous active GTP-bound GTPases and cytosolic inactive GDP-bound GTPases is regulated by guanine dissociation inhibitors or GDI-like proteins[73].

Previous studies in our laboratory have shown a link in expression between the TJ protein JAM-A and the focal adhesion molecule β1 integrin in breast cancer tissues[74]. Further investigations to tease out the potential molecular crosstalk between JAM-A and β1 integrin identified the Rho GTPase Rap 1 as an important intermediary in controlling breast cancer cell migration[75]. Attenuation or knockdown of JAM-A in MCF7 breast cancer cells reduced the expression of β1 integrin along with αv and α5 integrins, resulting in reduced cell migration. The data presented in this study suggests a mechanism whereby activation of Rap1 by

JAM-A occurs indirectly though association of JAM-A with the downstream signaling molecules Afadin (AF-6) and PDZ-GEF2, the guanine exchange factor[75]. Notably this mechanism was previously identified in SKCO-15 colonic epithelial cells, whereby loss of JAM-A, Afadin or PDZ-GEF2 resulted in decreased Rap1 and β1 integrin expression in addition to decreased cellular migration[76].

Another mechanism through which Rho GTPases could potentially influence crosstalk between cell-cell and cell-matrix junctions is *via* coincident inputs from structural proteins located at both sites. One such example is the cytoskeletal protein vinculin, which is recruited to (and localises at) both cell-cell and cell-matrix junctions[77] with a higher affinity for cell-matrix than cell-cell adhesion sites[78]. At the cell-cell junction, vinculin stabilises E-cadherin through binding with β-catenin[79] and strengthens actin binding by binding with α-catenin[80]. At the cell-matrix junction vinculin plays an important role in mediating cell signaling between cytoskeletal and ECM proteins *via* its role in focal adhesion formation[81]. Activation of vinculin at the cell-matrix junction requires binding to several proteins including talin and paxillin[81,82] with interaction of active vinculin and paxillin being dependent on Rac1 activation[83]. Additionally, active vinculin is important with respect to cell-matrix adhesion *via* stabilising adhesion complexes and promoting integrin clustering[84]. Vinculin has also been implicated in facilitating membrane protrusion *via* extension of lamellipodia and cell spreading, following binding and recruitment of Actin-related protein (Arp) 2/3 to sites of integrin clustering[85]. Of interest, the formation of the vinculin/Arp 2/3 complex was found to be regulated by PIP2 (phosphatidylinositol-4,5-bisphosphate) and Rac1[85]. While research to date has mainly investigated the role of vinculin in the cell-matrix context, further investigation is warranted to investigate if Rac1 can directly regulate vinculin functionality at the cell-cell junction, thereby offering a potential common pathway through which vinculin can elicit its functions and mediate crosstalk between adhesion sites.

MAGI-1 (MAGUK with inverted domain 1) is a scaffolding protein containing a PDZ domain which has been shown to regulate structural and functional features at the cell-cell junction and to increase cell adhesion to matrix proteins[86,87]. Interestingly, MAGI-1 is required for vascular endothelial-cadherin-dependent Rap-1 activation, which, upon activation facilitates relocation of vinculin from the cell-ECM location to the cell-cell location thereby regulating AJ formation[88]. MAGI-1 is known to stabilise E-cadherin and β-catenin localisation at the AJ, which in turn increases actin stress fiber and focal adhesion formation. MAGI-1 has been implicated as a putative negative regulator of metastasis in a colon cancer model, whereby overexpression of MAGI-1 was shown to increase integrin-mediated cell adhesion to matrix proteins and outside-in signaling *via* FAK, ERK 1/2 and Akt, and to inhibit anchorage-independent growth, invasion and migration in addition to Wnt signaling[87].

This study proposes a mechanism whereby inhibition of cyclooxygenase-2, which is overexpressed in a number of cancers (including colon), upregulates MAGI-1 which in turn inhibits Wnt/β-catenin signaling by decreasing free β-catenin[87]. As such MAGI-1 identifies itself as an important regulator of cell-cell and cell-matrix functions and signaling.

Nectins have been identified as important molecules capable of co-operatively communicating between cell-cell and cell-matrix junctions *via* their role in integrin-cadherin crosstalk. Nectins are Ig-like cell adhesion molecules which regulate the formation of cell-cell junctions, including TJs and AJs[12]. Nectins have been shown to regulate cellular features including cell polarity, proliferation, movement and survival[89], the deregulation of which is implicated in cancer. Nectins can physically interact with the αvβ3 integrin at cell-cell adhesion sites, leading to activation of Src kinase which is required for the formation of cadherin-based AJs[90]. Src is also activated by nectins following nectin-nectin interactions at cell-cell contact sites, which induces activation of the GTPase Rap1, resulting in downstream activation of the other GTPases Cdc42 and Rac[90]. Cdc42 activation results in filopodia formation, while Rac activation leads to lamellipodia formation[91], important structures for cell migration and movement[92]. This identifies a potential mechanism whereby activation of Rap1 by nectin-based cell contact can influence actin dynamics at the cell-matrix interface, which in turn regulate functional behaviours associated with migration. Additionally, interactions between integrins and Rho GTPases can elicit pro-migratory functions, as integrins are known to activate the Rho GTPases Rac and Cdc42[93] with Cdc42 being shown to drive trans-endothelial migration of cancer cells by enhancing the expression of β1 integrin[94], an important process in metastasis. The versatility of Rho family GTPases in driving diverse signaling events clearly illustrates their potential to influence mammalian physiology and pathophysiology. However an intriguing aside is that mammalian Rho GTPase signaling is also commonly exploited for non-mammalian advantage, specifically in invasion or intoxication strategies of multiple bacterial pathogens. Interested readers are referred to an excellent recent review on this topic[95], while the next section of this manuscript will instead concentrate on the concept that pathogenic interactions with mammalian cells represent a paradigm of successful crosstalk between cell-cell and cell-matrix adhesion sites.

Pathogenic infection as a paradigm for inter-junctional crosstalk

By virtue of their strategic bridging location between the apical and basolateral membrane domains of epithelial cell surfaces, it has been well-established that TJ proteins are attractive targets for pathogens seeking to infect cells or to modify cellular functions towards a survival advantage. Among those TJ components known to be directly exploited as viral pathogen receptors or co-receptors are JAM-A (reovirus[96], rotavirus[97]) and

CAR (adenovirus 5, group B coxsackieviruses[98]), but many non-viral pathogens are also recognised to use TJ disruption as a broader primary mechanism to open up access to basolaterally-located attachment receptors (*e.g.*, *Yersinia*[99]) or to orchestrate signaling events that drive disease [*e.g.*, *Helicobacter pylori* (*H. pylori*)[100]]. An emerging literature is revealing that pathogens are masters of inducing crosstalk between epithelial cell-cell and cell-matrix adhesive interfaces to facilitate their own goals, of which various examples will be discussed herein.

In the case of viral infection of epithelial barriers, cell entry is a key requirement, and abundant examples illustrate cooperativity between cell-cell and cell-matrix sites to facilitate an attachment-invasion sequence. JAM-A has been described to act as an attachment receptor for the *Reoviridae* family member rotavirus *via* its VP4 spike protein[97], in conjunction with integrins acting as post-attachment receptors for the same non-enveloped virus[101]. Furthermore gene silencing screens have identified a potential role for not just JAM-A but also claudins-6, -9 and -14 in mediating rotaviral infection of cells[102]; which fits with the observation that a component of the VP4 spike (VP8) has sequence homology to the extracellular loops of claudin and can diminish TJ gate and fence function[103]. Compromising the paracellular barrier in this fashion would confer a distinct advantage upon the ability of the rotavirus to access basolaterally-located integrin co-receptors; which it could then bind *via* opportunistic expression of integrin-recognition tripeptide sequences in its outer capsid[104]. Accordingly, multiple viruses including the human cytomegalovirus[105] have been demonstrated to possess classic integrin binding sequences.

Another *Reoviridae* family member which has been shown to orchestrate crosstalk between cell-cell and cell-matrix sites to facilitate infection (and thereby survival) is the reovirus. Specifically, reovirus uses JAM-A as its cellular attachment receptor[96], whereupon β1-integrin is required for viral internalization *via* interactions with RGD/KGE sequences on the λ2 reovirus protein[106]. It is interesting to note that that the reovirus attachment protein sigma1 can, *via* a higher affinity interaction, substitute for one molecule of JAM-A in the homo-dimerisation event which characterises the adhesive function of JAM-A[107]. This could have implications for the integrity of the epithelial barrier which would, in turn, modify pathogen access to the normally restricted sub-epithelial compartment.

The final example of virus-induced adhesive crosstalk which will be discussed here is that of coxsackie and adenoviruses. A protein member of the Ig superfamily which is structurally related to JAM-A, namely coxsackie and adenovirus receptor (CAR), has been identified as the attachment receptor for both adenovirus-5 (Ad5) and group B coxsackieviruses[98]. However it has been demonstrated that post-attachment internalization of adenovirus depends upon interactions between virally-expressed RGD sequences and alpha-V integrins[108].

Accordingly, CAR overexpression can modify the activation status of integrins *via* activation of p44/42 MAP kinase, which concomitantly enhances cell-matrix adhesion and Ad5 infection[109]. Intriguingly, a feedback loop whereby Ad5 infection also promotes CAR dimerization and further MAPK-dependent viral infection[109] supports the assumption that infection dynamics are critically regulated by crosstalk between cell-cell and cell-matrix sites. Given that both CAR and integrin expression levels are sensitive to modulation by certain cytokines[110], it is likely that the specific environmental milieu of a tissue can influence not only adhesive crosstalk but consequently the likelihood of infection.

Mechanisms of infection differ somewhat in the context of bacteria, which, unlike viruses, are not entirely dependent on cellular invasion for their propagation. However a recurring theme is that bacteria often disrupt cell-cell junctional barriers to access basolaterally-located receptors, facilitating injection of bacterial proteins into host cells. One such example is *Yersinia pseudotuberculosis,* which has been shown to attach to a pool of β1-integrin that co-localizes with ZO-1 at TJ of renal epithelial cells[111]. The seemingly incongruous spatial overlap of a cell-cell and cell-matrix protein may, in this case, be explained by disruptions in F-actin and the redistribution of actin-affiliated cell-cell adhesion proteins following cellular penetration of the cytotoxic *Yersinia* outer membrane protein YopE[111]. Alternatively an environment of acute inflammation could promote access to basolaterally-located β1-integrin, as it has been demonstrated that colonic epithelial cells become sensitized to *Y. pseudotuberculosis* infection following the induction of micro-discontinuities in sites where neutrophils have trans-migrated across the epithelial barrier[99]. A pro-inflammatory cytokine balance could also perturb cell-cell adhesion and barrier function in a manner that permits pathogen access to basolateral receptors, as it has been demonstrated that IFNγ causes internalization of the tight junction protein occludin *via* macropinocytosis[112]. Interestingly, selective macropinocytosis of occludin has been illustrated downstream of Coxsackievirus B binding to CAR at TJ, with a block on viral entry in the absence of either occludin or a functional macropinocytotic pathway[113]. The nature of occludin as a common target for some bacterial and viral infections is further evidenced by a report that the *E. coli*-derived bacterial toxin cytotoxic necrotizing factor-1 (CNF-1) induces occludin and ZO-1 internalization *via* an uptake pathway involving caveolar lipid rafts[114]. In light of the crosstalk mediators alluded to in previous paragraphs, it is no coincidence that CNF-1 simultaneously activates Rho, Rac and Cdc42 in conjunction with impairment of epithelial barrier function and putative activation of focal adhesion assembly[114].

The final example of bacteria inducing inter-adhesion site crosstalk which will be dealt with in this review is that of *H. pylori*, the causative organism of peptic ulcer disease and itself a Group I carcinogen. The *H.*

pylori effector protein CagA has been shown to disrupt TJ integrity by way of forming a complex with JAM-A and ZO-1[100]. Furthermore another gene in the *cag* pathogenicity island, CagL, reportedly binds to αV-β1-integrin *via* an RGD sequence, simultaneously activating FAK and Src activation whilst facilitating CagA entry into cells[115]. Taken together, such examples of cooperativity between cell-cell and cell-matrix adhesion sites make it intriguing to speculate that the crosstalk mechanisms which pathogens have evolved could be exploited for therapeutic advantage in not only infection but also cancer contexts.

THERAPEUTIC TARGETING OF PUTATIVE CROSSTALK MEDIATORS

Kinases as drug targets in cancer

Tyrosine kinase signaling is frequently deregulated in both solid and haematological tumors, and has been solidly linked to tumor initiation and progression. Both receptor and non-RTKs could mediate crosstalk signals between cell-cell and cell-matrix adhesion sites. In cancer cells RTKs are often constitutively active, and drug-based targeting of RTKs will only be successful if the targeted RTK is a major regulator of cancer cell survival. The most commonly deregulated RTKs include EGFR, HER2, MET, VEGFR, PDGFR, FGFR and IGF-1R[116]. Accordingly several monoclonal antibodies and small-molecule inhibitors have been developed to target these receptors. Since EGF receptor family members are frequently overexpressed in breast cancer patients[117,118], monoclonal antibodies like Trastuzumab (Herceptin), pertuzumab (Omitrag) and small-molecule inhibitors like lapatinib, gefitinib, erlotinib, AEE788 and CI-1033 have formed prototype targeted therapies[119]. For more detailed information on EGF receptor family members and their inhibitors, interested readers are directed to the following review article[120]. Further monoclonal antibody (pertuzumab) and small-molecule inhibitors (AEE788 and CI-1033) have been approved for clinical testing in various cancers like ovarian, prostate, and non-small cell lung cancer (NSCLC) whereas small molecule inhibitors (gefitinib and erlotinib) have been approved for treating NSCLC.

Another attractive option for targeted therapy in cancer has been the non-RTK Src, whose expression is known to be elevated in several tumors and has been implicated in disease progression, invasion and metastasis. Among the non-RTKs Src has been one of the most widely studied, encompassing its family members Lyn, Fyn, Lck, Hck, Fgr, Blk, Yrk, and Yes. To date several Src inhibitors such as dasatinib, SKI-606 (Bosutinib), and AZD0530 have been developed and are undergoing clinical trials in breast cancer patients[121-126]. Dasatinib is an effective inhibitor of several kinases including Bcr-abl, Src family kinases, c-KIT and PDGFR-β5[127], with promising preclinical results indicating its ability to inhibit the growth of breast luminal and basal tumors independently of ER or HER2 status[128,129]. Analogously, SKI-606 inhibits several Src family kinases and Bcr-Abl and suppresses migration and invasion of breast cancer cells[130]. AZD0530 (Saracatinib) is a more selective inhibitor of Src and Bcr-Abl in gastric and prostate cancer[131,132], and in breast cancer (when combined with estrogen blockers) has been shown to inhibit proliferation of cancer cells *in vitro* and *in vivo*[133].

Since both receptor and non-RTKs are frequently overexpressed in tumors and play key roles in signaling crosstalk, this section has highlighted the logic of targeting their signaling for downregulation as a mechanism of stalling cancer progression. However it must always be remembered that cancer is a complex disease resulting from deregulation of several signaling pathways, whether concurrently or sequentially, therefore long-term therapeutic strategies must always consider targeting multiple signaling pathways for the most effective outcome.

Rho GTPases as drug targets in cancer

Activation of Rho GTPases and their interactions with multiple different molecules can initiate many signaling pathways and downstream effects, including cancer-related behaviours such as migration, proliferation, cytoskeletal changes and apoptosis[134]. As such, Rho GTPases present themselves as attractive therapeutic targets, and many endeavors have been made to target these molecules in cancer, with promising preclinical results so far[134]. A Rac-specific small molecule inhibitor, NSC23766, has been found to inhibit features of invasion and anchorage-independent growth in human prostate cancer PC-3 cells[135]. Additionally, this compound was also found to inhibit breast cancer cell growth *via* cell-dependent mechanisms, either through cell cycle arrest or apoptosis[136]. Since then, several derivatives of this Rho GTPase inhibitor have been developed including AZA1 and AZA197.

A Cdc42 and Rac1 GTPase inhibitor, AZA1, a modified derivative of NSC23766, has been shown to inhibit migration and proliferation in addition to promoting apoptosis in prostate cancer cell lines *in vitro*[137]. This study also demonstrated increased survival and a reduction in tumor growth in a 22Rv1 androgen-independent xenograft model of prostate cancer[137]. In addition, another modified derivative of NSC23766 and a Cdc42 inhibitor, AZA197, has been shown to inhibit proliferation, migration and invasion in addition to exhibiting pro-apoptotic functionality in human colon cancer cell lines *in vitro*[138]. In this study, AZA197 also inhibited proliferation and promoted apoptosis while decreasing tumor growth and increasing survival in a human colon cancer xenograft mouse model[138].

Additionally, two Rac specific inhibitors, EHT 1864 and EHop-016, have shown anti-tumorigenic properties in breast cancer. EHT 1864, a Rac-specific inhibitor, was shown to inhibit estrogen-mediated breast cancer cell proliferation and to decrease growth

of tamoxifen-resistant breast cancer cells[139] thereby identifying potential subtypes of breast cancer which this Rho GTPase inhibitor may preferentially target. In another study, EHT 1864 was also shown to have anti-proliferative, anti-invasive and pro-apoptotic effects in breast cancer cells[140]. The small molecule Rac inhibitor, EHop-016, has also shown promising preclinical results in targeting Rac activity in breast cancer. In one study, treatment with EHop-016 resulted in reduced tumor growth, inhibition of metastasis and angiogenesis in addition to inhibiting proliferation and increasing apoptosis in MDA-MB-435 breast cancer cells[141].

Rho GTPases have been shown to play a role in cell signaling and functions critical to tumor formation and metastasis. Interestingly, Rho GTPases, as discussed in this review, have been shown to interact with and activate molecules present at both the cell-cell and/or cell-matrix locations and may provide mediators of crosstalk between these cellular locations. As demonstrated in different cancer models, inhibition of Rho GTPases suggests a novel and potentially beneficial approach in cancer treatment and in the prevention of metastasis. It is interesting to speculate that targeting specific Rho GTPases which function at both the cell-cell and cell-matrix junctions may indeed offer enhanced inhibitory effects and present potential advantages over single site-directed inhibitors.

Pathogenic mechanisms as drug targets in cancer

We have already illustrated that enzymes (such as kinases and GTPases) offer huge potential as cancer drug targets by virtue of their capacity to modify cell signaling, including that between cell-cell and cell-matrix junctions. However there is also an emerging literature on the concept that pathogens which bind to (or interfere with) cell-surface adhesion receptors could be used as tumor cytolytic agents, drug delivery systems or even as immunomodulators in various cancers. The simplest argument is in the use of pathogens or their derivatives as cytolytic agents. This has been well-evidenced by the interaction of *Clostridium perfringens* enterotoxin (CPE) with its cellular receptors, the tight junction proteins claudin-3 or -4, having a cytolytic effect on claudin-overexpressing breast cancer cells[142] and also brain metastases of breast primary tumors[143]. Therapeutic potential of using CPE has also been suggested for ovarian[144,145], endometrial[146] and pancreatic[147] tumors. Similarly, the JAM-A-binding pathogen reovirus has been mooted as a potential therapy for certain brain cancers, although the mechanisms of cytolysis may yet be JAM-independent[148]. Furthermore targeting the CAR (CAR; a TJ-enriched Ig superfamily member related to JAM-A) with conditionally-replicating adenoviruses has been discussed in melanoma treatment[149]. Cytolysis aside, using pathogens or modified derivatives to deliver transgenes[150] or cytotoxic molecules (akin to the "magic bullet" concept with monoclonal antibodies) is also an interesting concept. Although not without conceptual

problems, some selectivity might be conferred by the careful selection of cancers in which the aforementioned pathogen receptors are known to be overexpressed. Finally the concept of immunomodulation *via* controlled pathogen attack of human cells also offers promise - from the very early observations of tumor regression in patients with certain *Streptococcal* infections (essentially a vaccination strategy involving the so-called Coley's toxin)[151] to the more recent report of differential sensitivity to infection of reoviruses expressing the co-stimulatory molecule B7-1[150]).

While a complete description of such phenomena is beyond the scope of this review, it is nonetheless intriguing to speculate that future developments in the arena of using pathogens or pathogenic derivatives to modulate cell-cell to cell-matrix adhesion site crosstalk (amongst other signaling mechanisms) may prove valuable in cancer therapeutics.

CONCLUSION

This review has endeavored to highlight pathways and signaling mechanisms of crosstalk between cell-cell and cell-matrix adhesion sites, with particular reference to the relevance of these concepts in cancer biology. Interestingly, successful crosstalk between spatially-distinct adhesion sites has been exemplified by the mechanisms which several pathogens use to invade or intoxicate epithelial barriers; and it is likely that much could be learned from such models in designing drugs to combat dysfunctional signaling crosstalk events associated with cancer progression. Some of the key putative mediators driving crosstalk between cell-cell and cell-matrix adhesion sites include Rho GTPases and kinases, hence these were concentrated upon in this review. Since Rho GTPases and kinases concurrently play a central role in tumorigenesis, we highlighted some current pharmacological strategies to target these molecules. We also alluded to the intriguing possibility of using modified bacterial or viral components as therapeutic tools to tap into crosstalk mechanisms which they have evolved mastery of. Taken together, we propose that rational strategies targeting specific regulators of cell-cell and cell-matrix adhesion may have far-reaching therapeutic potential in attenuating the signaling events associated with cancer initiation or progression.

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