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Crossroads of integrins and cadherins in epithelia and stroma remodeling

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Adhesion events mediated by cadherin and integrin adhesion receptors have fundamental roles in the maintenance of the physiological balance of epithelial tissues, and it is well established that perturbations in their normal functional activity and/or changes in their expression are associated with tumorigenesis. Over the last decades, increasing evidence of a dynamic collaborative interaction between these complexes through their shared interactions with cytoskeletal proteins and common signaling pathways has emerged not only as an important regulator of several aspects of epithelial cell behavior, but also as a coordinated adhesion module that senses and transmits signals from and to the epithelia surrounding microenvironment. The tight regulation of their crosstalk is particularly important during epithelial remodeling events that normally take place during morphogenesis and tissue repair, and when defective it leads to cell transformation and aggravated responses of the tumor microenvironment that contribute to tumorigenesis. In this review we highlight some of the interactions that regulate their crosstalk and how this could be implicated in regulating signals across epithelial tissues to sustain homeostasis.

Introduction

Epithelial tissues are highly specialized structures that shelter and separate body compartments. Their essential roles as protective barriers extend to additional fundamental functions including the absorption of solutes and nutrients, secretion and containment of body fluids. Epithelial sheets attach to their underlying basement membrane constituted by a supporting network of extracellular matrix proteins (ECM). Epithelia are generally non-vascularized and receive their nutrients and oxygen from the underlying connective tissue or stroma, which is constituted by different cells types including resident immune cells, fat cells, blood vessels, fibroblasts and their secreted ECM. Under physiological conditions, epithelial homeostasis is maintained via precise control of cellular proliferation, in which the interactions between epithelial cells, and their communication with the underlying stroma plays a fundamental role. Defects in the functional interactions between cells and in their crosstalk with the surrounding tissue microenvironment are associated with increased epithelial proliferation and cancer.

Epithelial cells connect to their epithelial neighbors by an array of intercellular adhesion complexes; these physically sustain the maintenance of the epithelial barriers, but also participate in a wide spectrum of signaling pathways that regulate cell behavior. These complexes include adherens junctions (AJs), tight junctions (TJs) and desmosomes. In addition, epithelial sheets attach to the underlying basement membrane through focal adhesion (FAs) and hemidesmosomes, which also provide signaling cues for the regulation of cell behavior, including cell polarity, proliferation and migration (Fig. 1).

All these specialized adhesion structures present a paradigmatic organization; they are constituted by transmembrane adhesive glycoproteins that physically link epithelial cells to the extracellular matrix or to neighboring cells. Adhesion receptors, through their cytoplasmic domain, interact with scaffolding proteins that anchor these complexes to different cytoskeletal structures, including actin filaments, microtubules and keratin intermediate filaments, thus preserving architectural integrity across epithelial sheets (Fig. 1).

Without diminishing the key roles of other junctions in sustaining epithelial architecture and homeostasis, FAs and AJs are of particular relevance. FAs are unique in promoting the attachment of epithelial sheets to the underlying basement membrane, and AJs are crucial to control the specificity of cell adhesion that coordinates cell sorting within tissues. In addition, AJs are the initiators of cell-cell contact formation and cohesive interactions, promoting the formation and maintenance of desmosomes and TJs. FAs and AJs maintain a dynamic biochemical and mechanosensory crosstalk toward the maintenance of epithelial architecture and function. FAs-mediated signals promote AJs-mediated cell cohesion by regulating the cytoskeleton and tension of epithelial cells. Reciprocally, AJs are also implicated in the regulation of the adhesive function of FAs in epithelia. In addition, their functions extend outside of the realm of epithelial cell adhesion and cytoskeletal organization, being implicated in an array of cellular processes including epithelial cell proliferation, migration, differentiation and apoptosis. The loss or failures in the regulation of FAs and AJs prevailing functional activity are causative of enhanced epithelial cell proliferation, loss of differentiation and the acquisition of tumorigenic and invasive characteristics.
Taken together, the crosstalk between AJs and FAs regulates the precision of dynamic cell changes and rearrangements of epithelial tissues during homeostasis. Importantly, these adhesion receptors sense signals arising from the microenvironment and coordinate transient increases in epithelial cell proliferation, regulated cell migration and local epithelial remodeling and differentiation to repair severed tissues in response to injury. When AJs and FAs are defective, these responses become unchecked, increasing the likelihood of epithelial diseases, including cancer.

However, our understanding of the contributions of FAs and AJs in sustaining epithelial homeostasis keeps broadening over the years. Several evidences indicate that the functions of some FAs and AJs proteins can no longer be strictly implicated only in the regulation of epithelial architecture and epithelial cell behavior. In this review, we highlight findings about the collaborative role of FAs and AJs associated proteins in integrating signals in epithelial cells and how they can participate in the communication with the surrounding tissue microenvironment. These signals regulate epithelial behavior and stromal cells responses, such as acute inflammation.

Figure 1. Complexes implicated in cell-cell and cell-matrix adhesion. Cell-cell adhesion complexes: in blue, tight junctions (TJs) composed by the transmembrane proteins occludins, claudins (1–24), junctional adhesion molecule (JAM A–C), and the cytoplasmic proteins zonula occludens (ZO 1–3), the cell polarity protein partitioning defective-3 (PAR3), MUPP1 and MAG1. In green, adherens junctions (AJs) composed by Cadherin and Nectin complexes. The transmembrane protein E-cadherin binds to the cytoplasmic proteins p120 catenin, α-catenin and β-catenin, whereas Nectin binds to afadin. In orange, desmosomes are constituted by the transmembrane proteins desmoglein (DSG 1–4) and desmocollin (DSC 1–3), and the cytoplasmic proteins plakoglobin (JUP), plakophilins (PKP 1–3) and desmoplakin (DSP) that anchor to intermediate filaments. Cell-matrix adhesion complexes: in red, the hemidesmosomes (HD), formed by the transmembrane α- and β-integrins and the cytoplasmic proteins BP180, BO230 and plectin. In purple, the focal adhesion complex (FAs), composed by the transmembrane α- and β-integrins and cytoplasmic scaffolding proteins that associate to the actin cytoskeleton.
inflammation and angiogenesis, to fulfill a balanced epithelial proliferation and differentiation, migration and tissue repair. Alterations in FAs and AJs may result in a chronic “activation” of the stroma. This involves changes in the expression of ECM proteins, ECM degrading enzymes, growth factors and cytokines, that promote angiogenesis, inflammatory recruitment and the differentiation of fibroblasts into myofibroblasts, which in turn sustain growth-promoting signals involved in tumorigenesis.2 Thus, when the signals mediated by some FAs and AJs proteins are defective, alterations in epithelial adhesion and homeostasis take place, and the “activation” of stromal cells cannot resolve, promoting uncontrolled epithelial proliferation, genetic mutations, evasion of senescence and apoptosis that lead to disease states, including carcinoma formation and metastatic spread. These findings are of clinical interest and are providing novel insights about the molecular mechanisms regulated by FAs and AJs that not only influence epithelial behavior but also the tissue microenvironment, and their implications in epithelial physiology and disease.

**Molecular Composition of Focal Adhesions and Adherens Junctions**

**Focal adhesions.** Epithelial sheets anchor to the underlying basement membrane that approach them to the stroma, via dynamic complexes formed by integrin receptors (Fig. 1). Epithelial integrin receptors form two different types of junctions, FAs linked to the acromosin cytoskeleton, and hemidesmosomes that are linked to intermediate filaments.6,15,16 FAs are present in most epithelial tissues, whereas hemidesmosomes are mainly found in skin.15-17 While the roles of FAs are better defined, the mechanical and signaling properties of hemidesmosomes are still poorly understood.

At the molecular level, integrin receptors are non-covalently linked heterodimers of α- and β-integrin subunits (Fig. 1). In FAs, the extracellular domain of these glycoproteins physically links cells to the ECM, and the cytoplasmic domain binds to scaffolding proteins that strengthen cell adhesion through their associations with the actin cytoskeleton, such as talin, kindlin, vinculin, α-actinin and paxillin.18-21 The heterogeneous combination of the different α- and β-subunits identified to date determines the integrin receptor type and the binding specificity of epithelial cells to diverse ECM ligands, including fibronectin, laminins and collagens.22 This binding is not only involved in the mere physical attachment of cells to their substrates, but it also stimulates the signaling activity of the integrin receptors (affinity), which upon binding undergo conformational changes and integrin clustering (avidity).12 Indeed, it is well established that cell morphology and function can be controlled by the stiffness of the extracellular matrix.23,24 Integrin receptors present both “outside-in” and “inside-out” signaling properties. “Outside-in” signaling occurs when the integrin receptor binds to its ligand and the signal is transmitted from the integrin receptor into the cell. “Inside-out” signaling refers to the shift of integrins between low- and high-affinity conformations that modulate their ligand binding.21 The “inside-out” properties of integrins are regulated by external stimuli that are transduced intracellularly. These signals modulate the direct binding of regulatory proteins, including talin and kindlins, to the short cytoplasmic domain of integrins, and induce a shift in the activation state of integrins.21 Several signaling transduction proteins are localized in FAs, including focal adhesion kinase (FAK), sarcoma kinases (Src), Abelson kinases (Abi), integrin-linked kinase (ILK) and small GTPases of both Ras and Rho families, including Rap1, Rac1, Cdc42 and Rho GTPases.25,26 Thus, integrin receptors act as sensors allowing cells to respond to different cues arising from the surrounding environment, instructing epithelial cells to change their behavior, including cell proliferation, cell survival and migration, in order to sustain tissue homeostasis.27-33

**Adherens junctions.** AJs localize at the boundary of epithelial cells, and they are highly dynamic structures constituted by two different types of junctions, Cadherin-catenins complexes anchored to cortical actin and microtubules34 and Nectin-afadin complexes anchored to the actin cytoskeleton (Fig. 1).35 Classical cadherins are transmembrane glycoproteins that promote homophilic interactions between cells via their extracellular domain, constituted by five cadherin repeats (ECs), in a Ca2+-dependent manner.36 E-cadherin is predominantly expressed in epithelial cells, and through its highly conserved cytoplasmic domain binds to the armadillo-repeat proteins β-catenin and p120-catenin,37 γ-catenin/plakoglobin, a β-catenin homologous protein, primarily associated with desmosomes, also associates to classical cadherins, and it can functionally substitute β-catenin when β-catenin is limited or modified.39,40 In turn, monomeric α-catenin binds to the complex via its interaction with β-catenin and indirectly anchors AJs complexes to the actin cytoskeleton,41,42 through its connections with actin-binding proteins such as Eplin, vinculin and α-actinin.43-45 While further work is needed to understand the complexity of the actin organization machinery that dynamically integrates AJs to the actin-myosin cytoskeleton, the recruitment of several actin polymerizing proteins at adhesion sites is regulated by α-catenin,42,46,47 such as formin and vasodilator-stimulated protein (Vasp)/Enabled (Ena).46,49 In addition, other actin nucleating and remodeling proteins are recruited and activated at cell protrusion sites including Actin-related-proteins-2/3 (Arp2/3) and Cortactin proteins,47,49 as well as the family of small Rho GTPases (Rac1, Cdc42 and RhoA), which participates in the regulation of AJs and actin organization. This promotes AJs clustering, extension in the interphase of adhesion, and contact stabilization and strength, to achieve the formation of polarized epithelia, which involves dynamic interactions between different molecular players that have been documented in excellent reviews published elsewhere.51

The other component of AJs is the nectin-afadin complex, constituted by the family of transmembrane proteins referred to as nectins, which are immunoglobulin-like cell adhesion molecules that promote homophilic and heterophilic interactions between epithelial cells in a Ca2+-independent way.52 Nectins anchor to the actin cytoskeleton via ALL1-fused gene from chromosome 6 protein (AF6/afadin), an actin binding protein.53-55 These proteins are effectors of Rap1, a Ras-like small GTPase with an essential function in the formation of AJs.56 AF6/Afadin also binds
to α-catenin, providing a physical link between nectins and cadherins, which promotes the collaboration of these complexes during the formation and stabilization of AJs. In addition, AF6/Afadin binds to various cell junction proteins, including ZO-1 in tight junctions, thus, promoting the establishment of the intercellular junctional complex and polarized epithelia.

Adhesive Crosstalk between Epithelial FAs and AJs

Over the past decades it has been recognized that adhesion receptors cooperate to sustain epithelial architecture acting as sensors of signals arising from their epithelial neighbors or from the surrounding tissue microenvironment. These can be biochemical or mechanical inputs that are translated into intracellular signals to regulate different aspects of cell behavior including proliferation, differentiation, cell survival, cell polarity and migration. These tightly coordinated events allow morphogenesis, tissue remodeling and sustain epithelial homeostasis. But how these signals are coordinated through the cooperation of integrin and cadherin adhesions is not completely understood. Several molecular and biochemical analyses have identified a number of common dynamic connections with the cytoskeleton and with signaling effectors. Thus, despite different molecular structures, integrin and cadherin-mediated adhesions operate with common biophysical characteristics to transmit and respond to biochemical signals and mechanical forces across epithelia.

The interdependence of FAs and AJs has been observed in different systems. For example, mouse kidney epithelial cells deficient in α3β1 integrin fail to form the subcortical actin organization, and present a reduced AJs binding to α-actinin and anchoring to the actin cytoskeleton. In skin keratinocytes, blocking antibodies to β1- and α3-integrins delay the formation of cadherin mediated adhesion and epithelial sheet formation, but keratinocytes terminal differentiation is not impaired, consistent with the maintenance of cell-cell contacts in β1-integrin deficient mouse epidermis. These and other results overall suggest that integrins reinforce E-cadherin-dependent cell-cell adhesion. Conversely, reduction or loss of the functional activity of AJs proteins results in increased integrin expression and ECM adhesion. Some examples include the observations in cultured keratinocytes, in which blocking antibodies for P- and E-cadherin in differentiating keratinocytes, prevents the downregulation of integrin expression in differentiated cells. Furthermore, in mice with epidermal deficiency of both P- and E-cadherin, signs of actin disorganization are also evident, accompanied by an atypical expression of β4-integrin in the differentiated layers of the epidermis. These and other results imply the existence of an inverse relationship between the assembly/disassembly of cadherin- and integrin-dependent adhesive structures. Overall, the results mentioned above highlight the relevance of a tight coordinated control of cadherin-integrin crosstalk to maintain epithelial homeostasis and prevent tumor cells to progress to an invasive state.

Adhesive crosstalk between epithelial FAs and AJs: mechanisms and players. Among the events that are initiated by FA- and AJ-mediated adhesion, the reorganization of cytoskeletal networks is one of the major outcomes that takes place. This involves changes in actin filaments, microtubules and intermediate filaments. Although the molecular mechanisms that are involved in this response are not completely understood, a number of molecules have been implicated in this process. Despite the overwhelming diversity of players that have been documented to date, the ones that participate in the reorganization of the actin cytoskeleton are so far the best understood. Here we mention some of the actin cytoskeleton connections and signaling effectors that participate in FAs and AJs convergent signaling; these can be proteins that physically interact or modulate the actin cytoskeleton and link adhesion receptors to the peripheral cytoskeleton belt, including vinculin, α-actinin, Arp2/3 and cortactin, or a myriad of signaling proteins that are activated upon FA- and AJ-mediated adhesion including Src, FAK and small GTPases of both Ras and Rho families.

One of the first perceptions that indicate that FAs and AJs intersect in an integrated network is that they connect to the actin cytoskeleton through several common molecules, including vinculin and α-actinin. However, vinculin and α-actinin interactions at FAs seem to be more stable than at AJs. This may be explained by the fact that the dynamic recruitment of these common proteins to FAs and AJs seems to occur through different domains; indeed, vinculin binds to talin in FAs and is recruited through a different domain to cadherin-mediated adhesions in a β-catenin-dependent way, and activated by α-catenin during AJs formation.

Several other common actin regulators are recruited to FAs and AJs, such as the important actin nucleator complex Arp2/3. In FAs, Arp2/3 is recruited by vinculin, and at AJs it physically associates to E-cadherin upon direct E-cadherin ligation. At these sites, Arp2/3 regulates actin assembly and its disruption compromises membrane protrusions and cell attachment. These activities at FAs and AJs are coordinated by a key actin-binding scaffolding protein referred to as cortactin, which integrates all these dynamic actin networks in many cellular processes, including cell migration, endocytosis and cell adhesion.

Cortactin is also a key player that coordinates cell-signaling events and integrates cellular responses upon FAs and AJs formation. The activity of cortactin is modulated by phosphorylation of several kinases, but perhaps the best characterized is through the tyrosine kinase Src. This kinase also localizes to both integrin and cadherin adhesions, and it is transiently activated upon their engagement. Src is also implicated in coordinating signals between FAs and AJs, since overactivation of Src signaling can induce downregulation of E-cadherin by an integrin-dependent mechanism. However, much remains to be learnt about how Src phosphorylation regulates the crosstalk between FAs and AJs. Interestingly, it has been shown that cortactin binds to the AJs protein p120-catenin, which like cortactin, was originally identified as a Src kinase substrate. In addition, it has been observed that reductions of p120-catenin expression, which destabilize cadherin-catenin complexes and promote cadherin internalization along the endocytic pathway, lead to a decrease in FA formation and impair the recruitment of...
contortactin to adhesion sites. This may position cortactin along with p120-catenin in the cascade of events regulated by Src that coordinate the crosstalk between integrin-cadherin complexes.

The recruitment of Src to FAs can be promoted by FAK, which physically interacts with the cytoplasmic tail of β1-integrin. Of note, downregulation or suppression of FAK signaling has been also implicated in the crosstalk of integrin-cadherin adhesion, since its loss perturbs the assembly of cadherins complexes in HeLa cells. However, this has not been observed in epithelial tissues such as in FAK-deficient mouse epidermis and FAK-deficient mammary epithelia, although its loss confers resistance to tumorigenesis in both tissues. This is likely due to the expression of its homolog proline rich tyrosine kinase 2 (PYK2) that may compensate for the loss of FAK.

Src/FAK signaling has the ability to regulate membrane dynamics by modulating the activity of the small Rho-GTPases, which are so far the best understood mode of integration of FAs and AJs mediated signals. Small GTPases are subjected to a GTP/GDP exchange cycle in which specific guanine nucleotide exchange factors (GEFs) promote the exchange of GDP to GTP, thereby converting small GTPases into an active signaling competent form. In many cell types, Rac negatively regulates the activity of Rho, and the balance between these antagonistic activities is critical for the coordination of cell adhesion. Rac1 and Cdc42 are primarily involved in the formation of filopodia and membrane ruffles respectively, while RhoA generates myosin-based contractility and stabilizes membrane dynamics through the activation of several downstream effectors, including ROCK.

These events are activated upon both integrin and cadherin ligation. For example, at initial stages of E-cadherin ligation both Rac and Cdc42 activities are transiently increased, while RhoA activity is initially decreased over few hours. Rac inhibition significantly reduces the ability of cadherin ligation to induce actin assembly. When RhoA is inhibited, cells exhibit impaired spreading on fibronectin and decreased cell-cell adhesion. In the case of Cdc42, it has been shown that it limits Rho activation to prevent an excess of actin-mediated tension that otherwise will lead to loss of cell-cell junctions.

Several components of both FAs and AJs are implicated in mediating Rho GTPases signaling in an integrated crosstalk. For example exogenous expression of β1-integrin can activate RhoA and Rac1, leading to the disruption of cadherin-dependent cell-cell adhesion. Additionally, the AJs protein p120-catenin has been directly implicated in the regulation of Rho GTPases. When overexpressed, it decreases Rho activity while increasing Rac and Cdc42 activity. p120-catenin has been also implicated in the crosstalk between Rac and Rho through the recruitment of p190RhoGAP, a Rho inhibitor. This event may take place at AJs, coupling Rac activation to localized inhibition of Rho, which is essential for AJs formation. Interestingly, loss of p120-catenin leads to a constitutive activation of RhoA GTPase in fibroblasts and epithelial cells, which leads to an increase in FAs formation. This increase in FAs correlated with alterations in cell spreading, and cell motility in fibroblasts and in keratinocytes (Epifano and Perez-Moreno, unpublished data).

An additional key player in coordinating FAs and AJs communication is ILK, which is a serine/threonine kinase recruited to FAs via direct interactions with β1- and β3-integrin cytoplasmic tails. ILK activation is related to the stabilization of β-catenin, which has dual roles in AJs and the canonical Wnt signaling pathway. Upon ILK activation, β-catenin stabilization and nuclear accumulation can take place, along with the formation of the transcriptional β-catenin/Tcf complexes and the regulation of Wnt signaling effectors.

Finally, Rap1, the closest homolog of the small GTPase Ras, is also a key player in the dynamic integrin-cadherin crosstalk. Rap1 regulates the “inside-out” activation of integrin, and E-cadherin plays a major role in the “outside-in” regulation of Rap1. In these lines, the disruption of E-cadherin mediated contacts and its internalization by endocytosis leads to the activation of Rap1, which is associated with an increased Src kinase activity. Interestingly, the E-cadherin internalized vesicles do not contain p120-catenin, and of note, p120-catenin in the cytoplasm has been reported to modulate the activity of Rho GTPases. Upon cadherin internalization, the activated Rap1 mediates the formation of mature integrin-mediated adhesions. This has been related to the capability of Rap1 to regulate both recycling, avidity and affinity of integrins. These findings also suggest a major role of Rap1 in transmitting information from cadherin-based to integrin-based adhesive structures to couple cadherin inhibition to integrin activation during the remodeling of epithelial tissues.

Overall, these are some compelling evidences observed in epithelial cell lines, normal epithelial tissues and primary cells that indicate the existence of collaborative molecular networks between cell-cell and cell-matrix adhesions that sustain epithelial cell adhesion. The tight spatiotemporal regulation of the dynamic coordination of these connections is therefore fundamental for tissue architecture. FAs and AJs collaborative pathways also share the ability to influence different aspects of cell behavior, which are important for morphogenesis, the physiological balance of adult epithelial tissues, and with inherent implications in cancer.

**FAs and AJs as Integrated Modules that Sense and Respond to Signals Arising from Epithelia and Stroma**

The integrated mechanistic crosstalk of integrins and cadherins allow epithelial cells to respond to biochemical or mechanical inputs that are translated into intracellular signals to regulate the physiological balance of epithelial cells. The direct involvement of several FAs or AJs proteins in regulating several aspects of epithelial behavior, beyond the mere mechanical interconnection of cells, has been extensively documented in seminal publications that have been published over the past decades. Several FAs and AJs are bona fide tumor suppressors and oncogenes, and overall their loss of expression or normal functional activity correlate to different epithelial alterations depending on the epithelial system, ranging from loss of cell polarity, reduced or increased cell migration, increased or decreased epithelial proliferation, cell survival or apoptosis or circumvention of differentiation and senescence. These result in
defects that can perturb epithelial morphogenesis, loss of tissue function and have very important implications in cancer. In this regard, one of the most profound alterations that take place by defective FAs or AJ's adhesive properties, expression or signaling is the occurrence of epithelial-to-mesenchymal transition (EMT), which is a complex molecular program involved in morphogenesis and cancer that results in a gain of migratory and invasive characteristics. The readers are referred to some of several excellent reviews published elsewhere covering different aspects of cell behavior regulated by FAs or AJs during epithelial homeostasis and cancer.127-133 In this section, we will highlight some examples of how the integrated crosstalk of FAs and AJs in epithelial cells can sense and respond to signals that arise from the underlying stroma, and boost both epithelial and stromal responses to sustain homeostasis, and when defective may lead to cancer (Fig. 2).

Epithelial cells are able to present dynamic spatiotemporal changes in phenotype and function referred as to "plasticity." They also display "reciprocity" characteristics, which is the ability to process signals from the environment.14,134-137 These events are fundamental during tissue remodeling processes such as morphogenesis and wound healing, which are tightly controlled and with well-defined phases. During these events, transient increases of cell proliferation, collective cell migration and epithelial remodeling are observed to reestablish a functional epithelium,138 and are unrestrained in cancer cells.136 This has led to the establishment of parallels between tumors and a defective perpetuating process of wound repair.139

Upon injury, cellular junctions are severed, and AJs undergo a dynamic assembly and disassembly state that needs to be coordinated to integrin activation and adhesion to the ECM. This process requires the remodeling of the actin cytoskeleton and microtubule networks to allow epithelial spreading and polarized collective cell migration on a temporary secreted ECM toward the maintenance of tissue architecture. Interestingly, in Xenopus laevis it has been recently observed that keratin intermediate filaments can associate to plakoglobin at AJs and regulate collective cell migration.140 The contributions of this binding to the regulation of the affinity of integrins, perhaps through scaffolding proteins including plectins, is an important line of future investigation.

If the integrated crosstalk between FAs and AJs is perturbed, it can lead to important changes in cell behavior (Fig. 2). Indeed, the reduced strength of both cadherins, and switch in the expression of integrins and FAs attachment to ECMs,141-143 can result in increased individual cell migration, which can be mesenchymal or even switch to an ameboid state that is FAs independent.144,145 Epithelial repair upon injury also includes an acute inflammatory response and recruitment of immune cells and changes in the underlying connective tissue, including the formation of blood vessels, activation of fibroblasts and changes in the ECM and secreted growth factors that actively participate in promoting wound healing. These responses also need to be tightly controlled, since their chronic activation contributes to cancer (Fig. 2).2 Different signals arise form the epithelial cells and the tissue microenvironment including members of growth factors (TGF-β, TNF-α, KGF and HGF), chemokines, interleukins, prostaglandins, matrix metalloproteinases, changes in ECM composition and the generation of reactive oxygen species,136,146,161 that can affect the activation state of cadherin and integrin adhesion receptors (Fig. 2).

FAs and AJs in epithelia and stroma communication: adhesion and signaling. The coordination of the FAs and AJs crosstalk modulated by Rho GTPases has been observed in several tissue remodeling events. For example, AJs breakage upon injury may induce the accumulation of p120-catenin in the cytoplasm, which in turn activates Rac and Cdc42, and cell migration.162 This is consistent with the observed roles of p120-catenin in cell migration, which could take place in a cadherin independent manner.163 Its causal involvement in this response has been observed in some transformed cell systems, including ovarian cancer cells, in which the loss of p120-catenin can block their migration.164 Interestingly, conditional loss of function studies in mice have identified another role for p120-catenin, which consist in regulating signals from epithelial cells that emanate to the stroma and prevent chronic inflammation in epithelial tissues, including skin,116 intestine,165 esophagus and stomach.166 This involves the Rho-dependent activation of the inflammatory mediator NFκB, chronic inflammation and cancer (Fig. 2).116,166,167 Conversely, upstream of p120-catenin, both epithelial growth factor (EGF) and hepatocyte growth factor (HGF) have been shown to induce cell scattering and relocalization of p120-catenin from the membrane to the cytoplasm activating Rho GTPase activity and changes in FAs. Interestingly, increases in RhoA have also been related to the activation of β-catenin mediated signals in keratinocytes, which results in tissue tension that induces epidermal hyperplasia and tumor growth.168

Loss of β-catenin in the epidermis has also been implicated in NFκB activation, inflammation and cancer, but mediated in part by Rac1 (Fig. 2).116,167 In addition, β-catenin null epidermal cells show enhanced migratory behavior, increased sensitivity to insulin growth factor stimulation (IGF) and elevated Ras and MAPK activity.170

β-catenin, through its function in Wnt signaling, has a key function in integrating signals arising from FAs to respond to changes in the surrounding epiderlia environment. In this line, as

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**Figure 2 (See opposite page).** A reciprocal and coordinated regulation of FAs and AJs in epithelial cells is involved in the crosstalk between epithelia and stroma. FAs and AJs share downstream signaling molecules, including Rho GTPases and Src, and interactions with actomyosin cytoskeleton, which contribute to the coordination of their adhesive network. Whereas FAs assembly is related to a strengthening of AJ-mediated adhesion, AJs disassembly is related to an increase of FAs-mediated adhesion. During tumorigenesis the coordinated crosstalk between FAs and AJs in epithelial cells is impaired, and may result in the chronic activation of the stroma (e.g., secretion of soluble factors, cytokines, chemokines, MMPs and changes in ECM composition). These can generate perpetuating signaling loops without a clear endpoint that, if unresolved, may lead to further epithelial transformation with gain of migratory and invasive characteristics. In this figure, some specific signaling adhesive modules are shown using color-coded annotations as well as their points of convergence.
we mentioned in a previous section, β-catenin can be stabilized and translocated to the nucleus upon activation of ILK.171 Interestingly, moderate increases in the normal ILK activity are sufficient to trigger Wnt signaling, downregulate E-cadherin expression in intestinal and mammary epithelial cells, and induce tumorigenic characteristics,172,173 that are triggered by the expression of the EMT transcription factors Snail and Slug (Fig. 2).174 Furthermore, transgenic mice expressing ILK in mammalian epithelia exhibits an accelerated tumor progression and an expansion of breast luminal progenitor cells.175 Conversely, its loss leads to reductions in the appearance of inflammation-related cancers in a tumor carcinogenesis protocol, which is related to decreased expression of MCP1 and the chemokine CCL2, limited ECM changes along with a scarce inflammatory response.176

β-catenin can also functionally associate to FAs through its interactions with the laminin receptor α3β1-integrin. Primary α3β1-integrin null cells fail to activate β-catenin upon TGFβ1 mediated signals, since in the absence of α3β1-integrin active-pSmad is unable to associate to β-catenin. Thus, this reduces the capability of the cells to respond to TGFβ1 and undergo EMT events.177

Non-canonical Wnt signals are also at the nexus of FAs and AJs mediated signals, and promote a coordination of signals along with the surrounding stroma. Wnt5, a prototype Wnt for β-catenin-independent signaling has been implicated in proliferation and inflammation. In Xenopus laevis, Wnt5 is able to stimulate fibronectin and AJs assembly in a Rac dependent way,178 thus regulating morphogenetic movements, whereas in mammalian cells, Wnt5 cooperates with integrin signaling to stimulate FAs turnover in migrating cells.179

FAs and AJs in epithelia and stroma communication: growth factors and ROS. Cadherin and integrin complexes interact, sense and respond to the activation of several growth factors, however, their coordinated modulation through TGFβ3 is so far the best understood. TGFβ3 not only activates integrins (Fig. 2), but also regulates the expression of numerous integrins and integrin-associated proteins.180,181 Both FAs and AJs also integrate the signals mediated by this factor. Some examples include the observations in keratinocyte cell lines, where it induces loss of cadherin mediated adhesion, elevated Ras and MAPK activity and associated proteins.180,181 Interestingly these effects are mediated by the activation of Rac1 and are accompanied by increase in cell migration and invasion, and the expression of the E-cadherin repressor Snail1 leading to EMT.183 Conversely, it has been shown that loss of TGFβ3 receptor II in epidermal cells leads to the development of squamous carcinomas of rectal and genital epithelia, which are normally proliferative and subjected to stress, but not in the normal epidermis. However, its loss promoted accelerated tumor formation in epidermis in a mutated Ras background. Interestingly, TGFβRII-null keratinocytes also display increased integrin-FAK-Src signaling and migration. These data are consistent with the dual roles of TGFβ3 attributed during tumorigenesis: it acts as a tumor promoter during cancer progression, and as a tumor suppressor at early stages of tumorigenesis.184 Of note, it is known that TGFβ also activates other signaling pathways including p38 MAPK, JNK and PI3K-Akt185,186 that have been involved in the secretion of cytokines and chemokines influencing the inflammatory tumor microenvironment,187 inducing angiogenesis188 and overall boosting the invasive properties of tumor cells.189

In addition, HGF has been involved in promoting cell scattering and key aspects of EMT.189,190 It has been observed that HGF induced-cell scattering is enhanced by collagen and fibronectin and increases integrin mediated adhesion. Interestingly, it has been suggested that the loss of cadherin-mediated adhesion observed upon HGF treatment, is not due to decreases in the functional E-cadherin adhesive properties, but rather to increased integrin mediated adhesion and actomyosin traction forces that may disrupt cell-cell adhesion.191

Another growth factor that can activate signals that are coordinated by both FAs and AJs is tumor necrosis factor α (TNFα, Fig. 2), which is one of the major mediators of inflammation and inflammation-associated cancers.160,192,193 TNFα has the ability to induce the phosphorylation of FAK, and regulate FAK-mediated signaling and coordinate enhanced tumor invasion.194 TNFα is expressed in both epithelia and stroma, along with other inflammatory mediators,195,196 thus increasing the responses toward tissue repair or cancer. Its activation can be mediated by the NFκB-Snail signaling pathway,160,192,197 JNK198 and/or Wnt/β-catenin.199,200

Finally, emerging evidence indicates that reactive oxygen species (ROS) may regulate the coordinated crosstalk of FAs and AJs.201 These are a number of reactive molecules and free radicals derived from molecular oxygen, such as hydrogen peroxide;201 which are produced during the mitochondrial aerobic respiration or by oxido-reductase enzymes and catalyzed oxidation of metals, and they are strong oxidants with potential deleterious effects. Their levels are highly increased in events such as fibrosis and inflammation, and in turn, they act as cellular messengers that participate in cell signaling and in the regulation of gene expression.202 In these lines, it has been proposed that ROS influence the “inside-out” signaling of integrins by inducing their conformational change and activation (Fig. 2).202 Of note, signaling proteins such as Rho GTPases and phosphatases are also target proteins of ROS. In addition, ROS can also modulate the stability of cadherin-mediated adhesions.201

Concluding Remarks

The crosstalk between FAs and AJs is involved in the regulation of dynamic cell changes and rearrangements of epithelial cells within tissues, and several evidences indicate that they embark in a “tug of war” to sustain epithelial architecture and homeostasis.12,123,62 However, their functions extend beyond the realm of cell adhesion to act as important sensors of the tissue microenvironment. This is of particular relevance, since epithelial tissues are non-vascularized and receive their nutrients and oxygen from the stroma. In this regard, FAs and AJs may act as integrated adhesive units to sense and respond to signals arising from the tissue microenvironment. Future research will provide more insights about how their integrated functions promote epithelia and...
stoma communication; however, evidence has emerged in the past years implicating several FAs and AJs proteins in the regulation of signaling pathways involved in this event. Through them, they can promote a dynamic crosstalk between epithelial cells and stroma to coordinate transient increases in cell proliferation, regulated cell migration, inflammation, epithelial remodeling and differentiation to sustain the physiological balance of epithelial tissues. We propose that when the coordinated crosstalk between AJs and FAs is defective, all these above responses become unchecked, increasing the likelihood of epithelial diseases, including cancer (Fig. 2). Interestingly, recent approaches to study the role of some of these proteins in the stoma, such as β-catenin or FAK, have also underscored their relevance in sustaining stromal function.203,204 This also has to be tightly modulated since chronic activation of the stoma including fibroblasts, endothelial cells, inflammatory cells and changes in the ECM responses and generation of ROS are related to cancer and metastasis dissemination. Thus, FAs and AJs may regulate the overall tissue context, and it will be interesting to learn how they coordinate different aspects in epithelial physiology and disease.

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