Cell–Cell Contact and Receptor Tyrosine Kinase Signaling

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The behavior of cells within tissues is governed by the activities of adhesion receptors that provide spatial cues and transmit forces through intercellular junctions, and by growth-factor receptors, particularly receptor tyrosine kinases (RTKs), that respond to biochemical signals from the environment. Coordination of these two activities is essential for the patterning and polarized migration of cells during morphogenesis and for homeostasis in mature tissues; loss of this coordination is a hallmark of developing cancer and driver of metastatic progression. Although much is known about the individual functions of adhesion and growth factor receptors, we have a surprisingly superficial understanding of the mechanisms by which their activities are coordinated.

The evolutionary transition to multicellularity was accompanied by the appearance of genes encoding classical cadherins and by the diversification of receptor tyrosine kinases (RTKs), which likely enabled organisms to overcome the new challenge of coordinating nutrient sensing with cell–cell communication (Nichols et al. 2012; Suga et al. 2012; Richter and King 2013). The powerful ability of RTKs to stimulate cell division is presumed to underlie their frequent mutation and deregulation in human cancer (Lemmon and Schlessinger 2010). However, in mammals and other organisms RTKs also have nonmitogenic functions that are critical during tissue morphogenesis and homeostasis and may make important contributions to cancer development and metastasis (Cheung et al. 2011; Appert-Collin et al. 2015; Malartre 2016). Mounting evidence indicates that a fundamental interrelationship between cell–cell communication and RTKs governs both their mitogenic and nonmitogenic activities. Early studies of this relationship identified mechanisms whereby RTKs influence cell–cell contacts, but subsequent studies have revealed that cell–cell communication also confers critical spatial and mechanical control on RTKs (McLachlan and Yap 2007; McClatchey and Yap 2012; McCrea et al. 2015). In this review we will consider both sides of this relationship and discuss how, as an interrelationship, its fine-tuning could be so critical in guiding morphogenesis and disease. We will restrict our discussion to cadherin-based adherens junctions and maintain a particular focus on the epidermal growth factor receptor (EGFR) as paradigms for considering the intricate partnership between cell–cell and biochemical cues and the

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role of that partnership in governing the interface between a cell and its environment.

MODULATION OF CADHERIN-BASED INTERACTIONS BY RTKS

Local Impact of RTKs at the Adherens Junction

Early appreciation of a functional relationship between cell–cell communication and RTKs came with the realization that cell–cell junctions are centers of tyrosine phosphorylation (Alema and Salvatore 2007; McLachlan et al. 2007). Indeed, RTKs localize to junctions and can regulate junction components but the functional impact of those events remains surprisingly poorly understood (Daniel and Reynolds 1997; Bertocchi et al. 2012; McCrea et al. 2015; Bertocchi et al. 2017). For example, RTKs can provoke phosphorylation of the core cadherin complex components β-catenin, α-catenin, p120 catenin, or cadherin itself, either directly or via the activation of cytoplasmic tyrosine or serine/threonine kinases such as Src, Abl, PAK, and CK1/2 (Hoschuetzky et al. 1994; Shibamoto et al. 1994; Ji et al. 2009; Bertocchi et al. 2012; Escobar et al. 2015). Many studies conclude that RTK-promoted phosphorylation of the cadherin complex weakens adhesion, by disrupting the association between the cadherin complex and the cortical actin cytoskeleton and/or by promoting endocytosis of the cadherin complex (Fig. 1) (Bertocchi et al. 2012; McCrea et al. 2015). Perhaps best studied is tyrosine phosphorylation of β-catenin, which, depending on the site, can disrupt its association with the cytoplasmic domain of various cadherins or with α-catenin, thereby severing the link between cadherin and actin and destabilizing junctions (Ozawa and Kemler 1998; Roura et al. 1999; Bonvini et al. 2001; Piedra et al. 2001, 2003; van Veelen et al. 2011). Alternatively, in fly epithelia, tyrosine phosphorylation can promote β-catenin turnover without a clear disruption of the cadherin complex; whether this impacts cadherin clustering, actin cytoskeleton association or endocytosis is not clear (Tamada et al. 2012). Reversal of these mechanisms may contribute to dynamic junctional remodeling; for example, β-catenin phosphorylation and endothelial junction disruption can be reversed via the dephosphorylating activity of the SHP2 phosphatase, whereas vascular epidermal growth factor receptor 2 (VEGFR2)-induced phosphorylation of VE-cadherin can be reversed by vascular endothelial protein tyrosine phosphatase (VE-PTP) (Nawroth et al. 2002; Timmerman et al. 2012).

Multiple studies suggest that RTK activation weakens adhesion by promoting cadherin endocytosis (Fig. 1) (Cadwell et al. 2016). Several broad pathways have been proposed; for example, EGF stimulation can promote E-cadherin internalization via either caveolin-mediated endocytosis or Rac-modulated macropinocytosis (Lu et al. 2003; Bryant et al. 2007), whereas hepatocyte growth factor (HGF) can promote E-cadherin endocytosis via mechanisms involving the activation of PI3K, ARF6 or regulation of Rho and Rac (Kamei et al. 1999; Palacios et al. 2001; Wang et al. 2009). Much less is known about the specific molecular mechanisms by which RTK activity triggers cadherin endocytosis. One mechanism could involve the phosphorylation-induced disruption of the interaction between cadherin and p120 catenin, because p120 association physically masks the binding site for endocytic adapters on the cadherin cytoplasmic tail (Brown et al. 2009; Ishiyama et al. 2010; Nanes et al. 2012). Studies of astrocytes suggest a way that such a mechanism could be fine-tuned in collectively migrating cells via an RTK-driven front-to-back gradient of p120 phosphorylation and N-cadherin endocytosis (described below; Fig. 2B) (Peglion et al. 2014). However, it has not been conclusively shown that RTK activation specifically dissociates p120 from the cadherin cytoplasmic tail. An alternative mechanism for RTK-triggered cadherin endocytosis involves VEGF-induced activation of PAK, which phosphorylates the VE-cadherin tail, resulting in the recruitment of β-arrestin and clathrin-dependent endocytosis (Gavard and Gutkind 2006, 2008).

These examples collectively point to a role for RTK-induced phosphorylation of the core cadherin complex in destabilizing adherens junctions (AJs) or promoting junctional re-

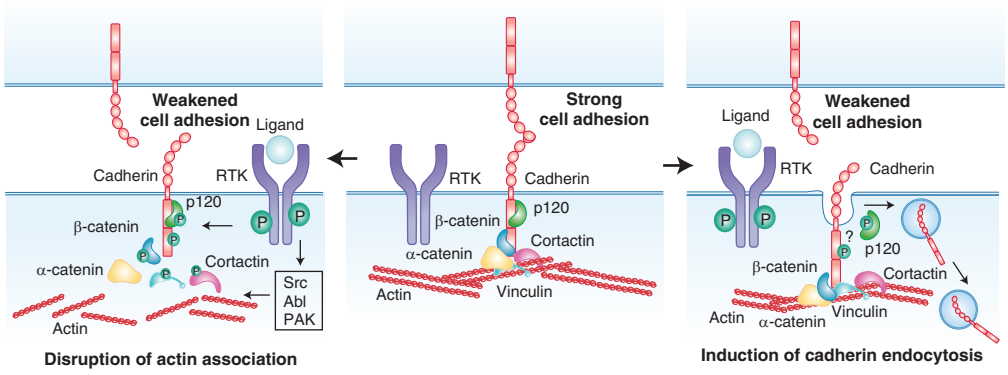

Figure 1. Mechanisms by which RTKs locally regulate the adherens junction complex. RTKs can phosphorylate multiple components of the adherens junction, either directly or through the activation of kinases such as Src, Abl, and PAK. These phosphorylation events are generally thought to weaken cell–cell adhesion, by disrupting the association of cadherins to the actin cytoskeleton (*left* panel), by inducing cadherin endocytosis (*right* panel), or both.

modeling. However, the influence of RTKs on cell junctions is likely much more complex. First of all, beyond the core cadherin complex, RTK activation can promote phosphorylation of multiple components of the larger supramolecular cadherin complex, which, in turn impacts adhesion stability and dynamics (Zaidel-Bar 2013). Recent studies highlight the role of vinculin tyrosine phosphorylation in the organization and mechanical responsiveness of cadherin-based junctions and identify the cytoplasmic tyrosine kinase Abl as a key regulator (Bays et al. 2014; Bertocchi et al. 2017). Similarly, appropriately regulated phosphorylation of the actin-binding protein cortactin is important for E-cadherin-based junction stability (McLachlan and Yap 2011; Truffi et al. 2014; Sroka et al. 2016). Both vinculin and cortactin function to organize dynamic actin rearrangements and tension at the cell junction, providing only a glimpse of the complexity of RTK-regulated protein interactions that confer dynamic yet mechanically durable properties to cell junctions (Fig. 1).

Activation of RTKs is likely to promote dynamic junction remodeling rather than acute disruption. Indeed, several studies have shown that RTK activity is also *required* for establishing or maintaining stable adherens junctions. For example, EGFR activity is necessary for the formation of continuous, circumferential E-cadherin-containing apical junctions in keratinocytes through its ability to activate the small GTPase Rac and promote membrane protrusions (Betson et al. 2002; Erasmus et al. 2015). Similarly, a recent study showed that EGFR activity is required for the establishment of interdigitating cell–cell boundaries, which have an important function in limiting cell "roaming" within mammary epithelial monolayers (Tang et al. 2014). In these cells inhibition of EGFR promoted linear junctional morphology and remobilized cells within the monolayer. Cells in tissues likely experience a continuous or graded, rather than on/off exposure to growth factors; thus the strength of RTK signaling may tune junctional remodeling during tissue morphogenesis or homeostasis.

Importantly, RTK activity can also influence adherens junctions indirectly via well-known impacts on cell-extracellular matrix (ECM) adhesion (Pruitt et al. 2014). This is illustrated by recent studies showing that HGF-induced cell scattering does not reflect a primary dissolution of cell–cell contacts, but instead the rupturing of cell–cell contacts that is secondary to changes in cell protrusion and cell-ECM traction that propel the migration of renal epithelial cells (de Rooij et al. 2005; Maruthamuthu and Gardel 2014). Mechanosensing at cell-ECM and

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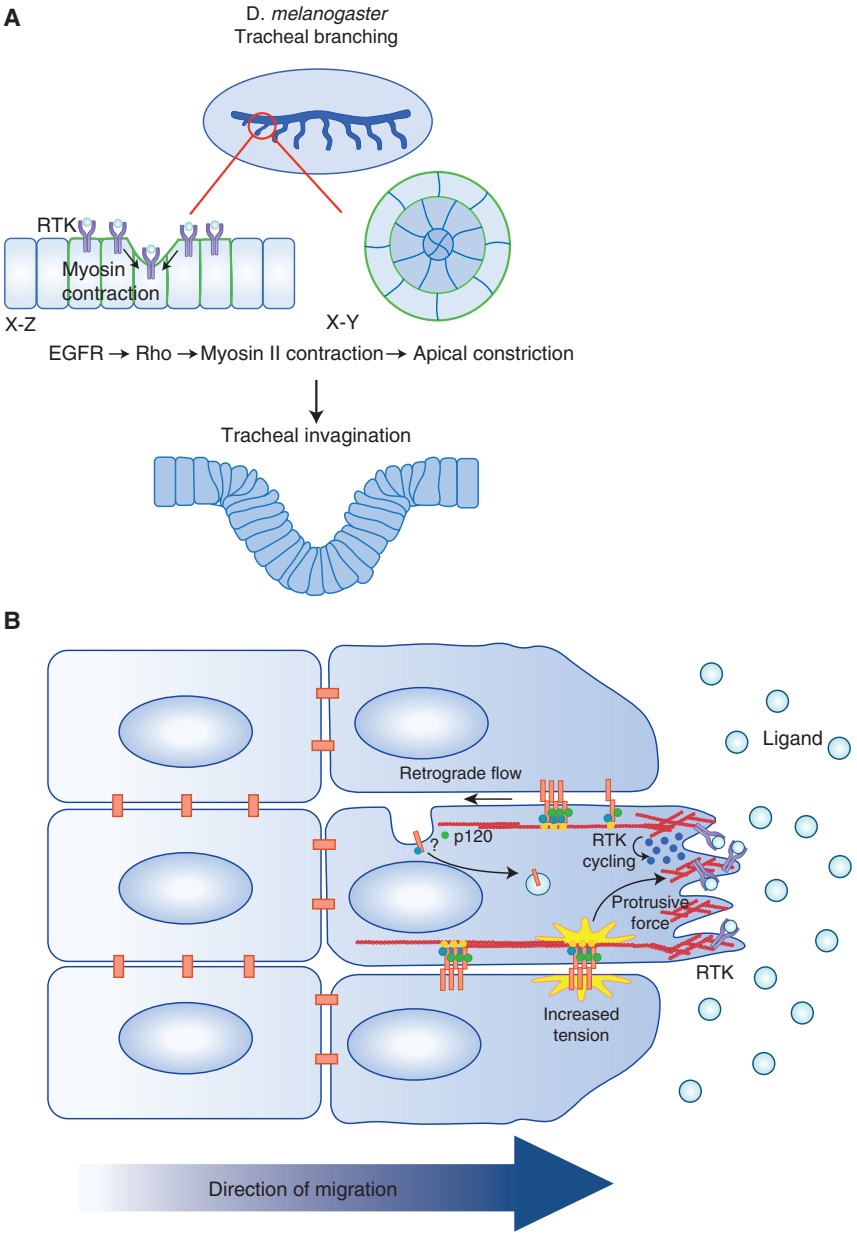

Figure 2. RTK regulation of cell–cell junctions has tissue-scale impacts. Increasing evidence suggests that RTKs regulate cell communication during morphogenesis and collective cell migration. (*A*) During the development of the tracheal system in *Drosophila,* epithelial invagination is driven by the coordination between cytoskeletal rearrangements and mitosis. A wave of EGFR activity is required for the localization of MyosinII (green) at cell–cell boundaries to form multicellular arcs. Actomyosin contraction along these arcs (arrows) leads to apical constriction and the intercalation of cells into concentric circles, and they invaginate. (*B*) Collective cell migration is dependent on the dynamic modulation of adherens junctions and is tightly coordinated with RTK activity. RTK signaling in the leading cell stabilizes protrusive forces that exert tension on AJs in a polarized fashion, thereby reinforcing the forward protrusion of the cell. Additionally, evidence suggests that collectively migrating astrocytes show a gradient of cadherin endocytosis that leads to the treadmilling of adherens junctions along the lateral boundaries of migrating cells. This gradient is mediated by glycogen synthase kinase (GSK)-induced p120 phosphorylation, which promotes cadherin internalization and polarized trafficking to the leading edge.

cell–cell contacts is tightly coordinated and RTK activity can significantly influence cell-ECM adhesions; therefore RTK-induced changes at one location likely impact the other (Friedl and Gilmour 2009; Maruthamuthu et al. 2011; Cai et al. 2014; Sim et al. 2015).

Tissue-Scale Impacts of RTKs on Cell Junctions

It is increasingly clear that RTKs regulate communication among cells during the sophisticated rearrangements that drive tissue morphogenesis. In particular, RTK-driven changes in actomyosin shape patterns of cell movement and organization in many different contexts. For example, formation of the tracheal placode in the fruitfly *Drosophila melanogaster* involves the rearrangement of epithelial cells into concentric rings, which is accompanied by apical constriction and a subsequent wave of coordinated mitoses that drive invagination (Fig. 2A) (Brodu and Casanova 2006; Nishimura et al. 2007). The intercalation of cells to form the concentric rings is achieved via EGFR-dependent alignment of nonmuscle myosin II (MyoII) along cell–cell boundaries to form multicellular arcs that direct centripetal invagination of the tissue. Notably, not only does MyoII arc formation and apical constriction largely fail in the absence of EGFR but subsequent mitoses occur prematurely, suggesting that changes in mechanotransduction via cell–cell communication are normally coordinated with cell division. In fact, appropriately timed mitotic rounding contributes to ordered tissue invagination in this setting (Kondo and Hayashi 2013). Interestingly, MyoII accumulation is highest along boundaries between EGF-high and EGF-low signaling cells in this setting, suggesting an intriguing mechanism of establishing/maintaining cellular heterogeneity within a tissue (Brodu and Casanova 2006; Nishimura et al. 2007). After placode invagination, tracheal morphogenesis proceeds via branching morphogenesis that is driven by a different RTK: fibroblast growth factor receptor (FGFR) (Brodu and Casanova 2006).

Instead of multicellular arcs, EGFR signaling is required for the planar polarized distribution of junctional MyoII that drives cell intercalation during the convergent extension-mediated elongation of the developing *Drosophila* renal tubules (Saxena et al. 2014). In this case, EGF produced at the distal tip of the tubule provides a polarized cue for planar orientation within the tubule. Similarly, in the developing *Drosophila* pharynx, EGFR drives the planar polarized distribution of MyoII along cell adhesions, which guides the alignment and oriented division of cells to form a highly ordered grid of square cells that confers mechanical strength to this dynamic tissue (Tamada and Zallen 2015). The impact of EGFR on actomyosin in these developmental contexts seems to reflect both transcriptional and posttranscriptional events, suggesting that EGFR may exert both acute and adaptive influences on cell–cell communication (Tamada and Zallen 2015).

In addition to patterning and morphogenesis within epithelial monolayers, RTKs and other chemokine receptors can direct changes in cell–cell communication that are critical for the coordinated or "collective" movement of cells (Fig. 2B) (Friedl and Gilmour 2009; Scarpa and Mayor 2016; Friedl and Mayor 2017). This type of movement drives many developmental processes, including branching or sprouting from epithelial tubes, as in tracheal, renal, or mammary branching morphogenesis or angiogenic sprouting; or the migration of isolated cell clusters such as *Drosophila* border cells, *Xenopus laevis* (frog) neural crest cells or the *Danio rerio* (zebrafish) lateral line primordium. In mature tissues, collective migration also contributes to epithelial wound healing and tumor metastasis (Friedl and Gilmour 2009). During collective migration soluble chemotactic factors, which often activate RTKs, can promote changes in cell–cell communication that facilitate coordinated cell movement (Scarpa and Mayor 2016). For example, collective migration of border cells in the fly ovary is driven by the chemotactic activation of two RTKs, PVR (a PDGF/VEGF receptor homolog) and EGFR in the leading cell of the cluster (Montell et al. 2012). Recent studies showed that RTK-driven tension on E-cadherin junctions at the front of a migrating collective, guide the polarized forward-protrusion

of the lead cell, and consequently the entire cluster (Fig. 2B) (Cai et al. 2014).

RTK-driven endocytic turnover of cadherins can also facilitate forward movement during cell migration (Fig. 2B) (Bruser and Bogdan 2017). For example, collectively migrating astrocytes show a gradient of cadherin endocytosis along the boundaries between migrating cells; cadherins are endocytosed preferentially at the rear of the cell–cell boundary and are recycled to the front, creating a treadmill that assists forward movement while maintaining adhesion between cells (Peglion et al. 2014). This polarized cadherin endocytosis is driven by a gradient of GSK3, which promotes phosphorylation of p120 cadherin at the rear of the cell–cell boundary; GSK3 is one of the few kinases that is negatively regulated by RTKs, suggesting a mechanism by which RTK-activating chemoattractants could guide the spatial turnover of cell junctions (Doble and Woodgett 2003). An intriguing possibility is that these mechanisms of generating polarized adhesion in migrating cells are linked and that RTK-induced junctional tension actually promotes cadherin endocytosis, perhaps preferentially at the rear (Fig. 2B). Notably, like the impacts of RTK activity on epithelial patterning described above, transcriptional mechanisms of RTK-induced junctional changes can also contribute to collective migration; for example, in addition to promoting mechanical tension and/or endocytic turnover of junctions, EGFR activity can influence E-cadherin levels during collective migration, thereby fine-tuning the levels of adhesion during this dynamic process (Lee et al. 2006; Lamouille et al. 2014).

CONTROL OF RTKS BY CELL–CELL JUNCTIONS

Spatial Control of RTKs by Junctional Cues

Cell–cell junctions can also govern the activity and spatial distribution of RTKs either indirectly or directly. For example, cell junctions provide positional cues that instruct the polarized distribution of receptors to apical or basolateral membranes, thereby controlling access to ligands that are either provided cell autonomously or from the microenvironment (Casaletto and McClatchey 2012). Simply imagined, cell–cell junctions could establish "fences" that prevent the diffusion of receptors across membrane compartments. However, mounting evidence suggests that cell–cell junctions provide more sophisticated positional and mechanical cues that guide the polarized delivery, retention or recycling of RTKs, yielding spatially distinct patterns of surface distribution. Early studies in *Caenorhabditis elegans* (worm) uncovered the importance of spatially controlling RTK distribution. The sole EGFR/ErbB RTK Let-23, plays a critical role in vulval development in worms (Simske et al. 1996; Kaech et al. 1998). Basolateral localization of Let-23 is necessary for vulval precursor cells to receive the EGF signal provided by the neighboring anchor cell and failure to localize Let-23 basolaterally results in a vulvaless phenotype (Schmid and Hajnal 2015).

Mislocalization of RTKs can also contribute to disease processes. For example, EGFR is primarily localized to the basolateral membrane along normal kidney tubules but the formation of renal cysts in human autosomal polycystic kidney disease (APKD) is nearly always associated with the abnormal apical distribution and autocrine activation of EGFR (Du and Wilson 1995; Orellana et al. 1995; Yoder et al. 1996). Notably, the mechanisms by which EGFR is basolaterally restricted appear to be distinct in the proximal tubules versus distal collecting ducts and involve association with different endocytic adapters such as AP1B or protein scaffolds such as IQGAP1; however, in vitro studies suggest that both mechanisms are controlled by the establishment of cell–cell junctions (Cotton et al. 2013; Banon-Rodriguez et al. 2014).

Equally important is the restricted distribution of ligands that can prompt autocrine activation of RTKs. For example, the failure to basolaterally restrict the EGF ligand, betacellulin, elicits the abnormal formation of lateral lumens and increased proliferation of cultured renal epithelial cells, both of which are dependent on EGFR activity (Singh et al. 2015). Importantly, mechanisms of spatially restricting RTKs and

their ligands can also be exploited dynamically in normal tissues. For example, injury of the airway epithelium and accompanying loss of cell junctions eliminates the normal segregation of basolateral ErbB receptors from their ligand heuregulin-α, allowing rapid ErbB activation to facilitate wound-healing (Vermeer et al. 2003).

Beyond the simple apicobasal patterns of RTK localization and activity that are established by junctional cues in polarized epithelial monolayers, a beautiful example of more specific compartmentalization involves luminally restricted FGF signaling in the zebrafish lateral line primordium (Fig. 3A) (Durdu et al. 2014). Collectively migrating epithelial cells deposit self-organized rosettes that serve as mechanosensory organs. Apical constriction and microlumen formation at the center of the rosette spatially organizes the secretion of the Fgf ligand such that it impacts only those cells whose apical surface contacts the microlumen. Cell–cell junctions delimit the microlumen and trap Fgf within it, restricting FGF receptor activation to this compartment (Durdu et al. 2014). Rosette formation contributes to the formation of many tissues in development and are often found in tumors suggesting that this mechanism may have much broader importance (Harding et al. 2014).

Collectively migrating cells also use junctions as cues to control the spatial distribution and activity of receptors (Scarpa and Mayor 2016). Migrating border cells in the *Drosophila* egg chamber express both PVR and EGFR; cell–cell boundaries guide the polarized distribution of RTK signaling in these cells, which is preferentially amplified at the front of the cell. This occurs via a poorly understood mechanism that likely involves endocytic recycling. Indeed, migrating border cells show a polarized distribution of both the recycling endosome and exocyst (Assaker et al. 2010; Wan et al. 2013).

Direct Association of RTKs with Junction Components

In addition to providing spatial cues that indirectly control the distribution of RTKs and their ligands, adhesion molecules can directly associate with and regulate RTKs. For example, E-cadherin can associate with EGFR in keratinocytes, and cell–cell contact is thought to stimulate transient activation of EGFR, driving Rac activation and junctional maturation (Hoschuetzky et al. 1994; Pece and Gutkind 2000; Betson et al. 2002; Erasmus et al. 2015). Alternatively, several studies argue that E-cadherin association impedes signaling from EGFR by reducing ligand affinity, mobility and/or internalization from the plasma membrane (Qian et al. 2004; Curto et al. 2007). Indeed, studies utilizing microspheres coated with the isolated extracellular domain of E-cadherin to specifically monitor the effects of E-cadherin engagement in the absence of a global cellular response to cell adhesion concluded that E-cadherin can inhibit EGFR activity at or near the plasma membrane in a β-catenin-dependent manner (Perrais et al. 2007). Similarly, association with VE-cadherin can block the internalization of VEGFR2 in endothelial cells (Lampugnani et al. 2006). For both EGFR and VEGFR2, cadherin-impeded internalization is thought to prevent signaling from internal compartments; in contrast, N-cadherin can associate with FGFR and PDGFR, which seems to also impede internalization but in this case the consequence is to enhance FGFR- or PDGFR-driven migration in breast tumor or fibrosarcoma cells (Suyama et al. 2002; Theisen et al. 2007). Thus the consequences of cadherin-RTK association may reflect receptor-specific differences in signaling from endocytic compartments.

Mechanical Control of RTKs by Cell–Cell Junctions

Minimal models that depict cell–cell contacts as spatial cues that direct RTK localization or platforms that physically engage RTKs are likely oversimplified. A growing appreciation of the complex cellular changes evoked by cell–cell contact suggests more complex mechanisms by which cells sense changes in cell–cell communication and modulate RTK signaling accordingly. An important example involves the transmission of mechanical forces in response to cell contact, which contributes to the phe-

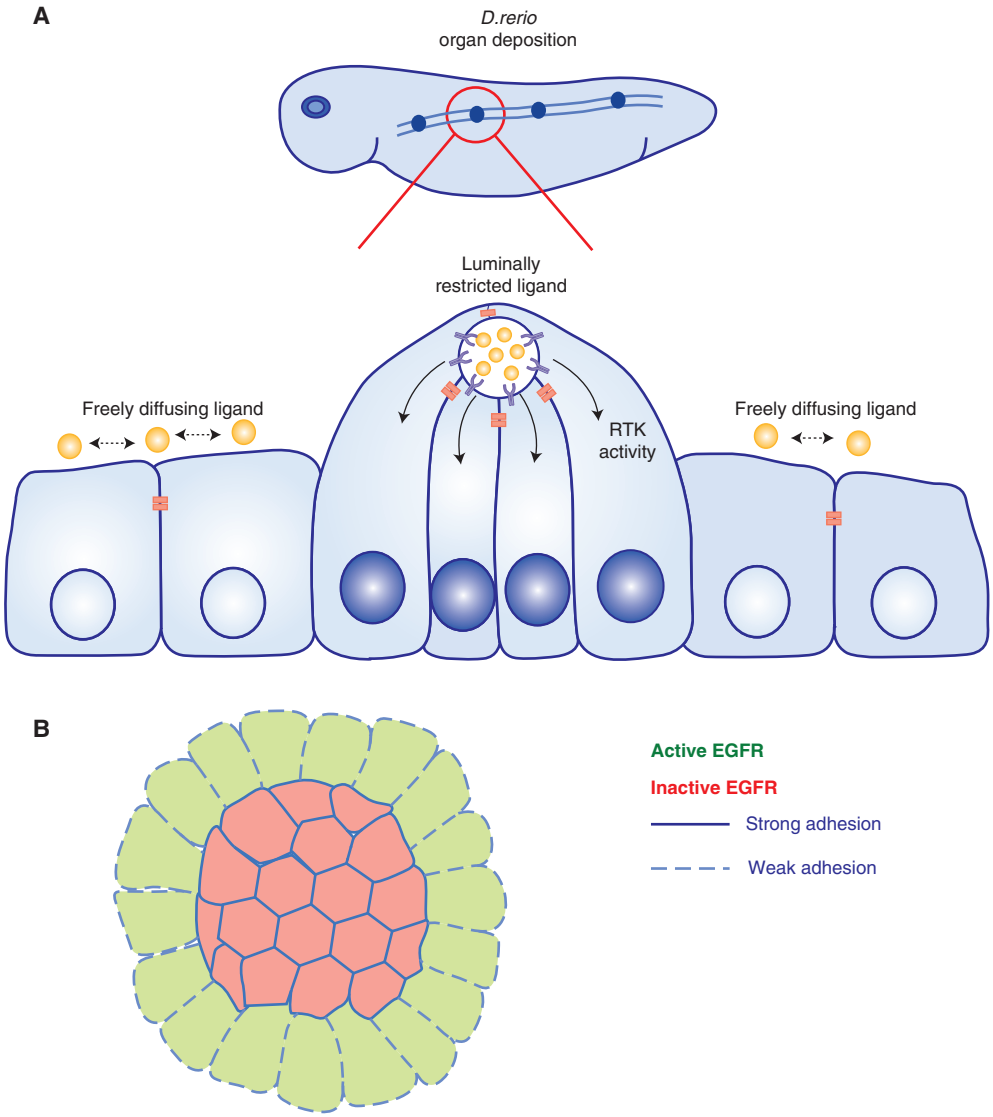

Figure 3. Control of RTKs by junctional cues. (*A*) Organogenesis in the *Danio rerio* lateral line primordium occurs through the sequential deposition of rosette-like mechanosensory organs by collectively migrating epithelial cells. Apical constriction and microlumen formation within the rosette restricts the secretion of FGF to the luminal cells, leading to the coordination and enhancement of FGF signaling in a feedback loop that regulates the frequency of organ deposition. (*B*) The transduction of mechanical forces in response to cell–cell contact can regulate the contact-dependent inhibition of cell proliferation through the control of EGFR signaling. Studies have shown that EGFR signaling is inhibited by the establishment of cell–cell contact through a mechanosensitive mechanism. This inhibition of EGFR can be overridden by experimentally increasing the forces exerted on adherens junctions.

nomenon of contact-dependent inhibition of proliferation in epithelial cells. This idea was supported by studies showing that EGFR signaling is inhibited in a graded manner in response to the amount of contact that cells sense (Fig. 3B) (Kim et al. 2009). Indeed, experimentally enhancing the force exerted on cell–cell contacts by increasing matrix stiffness sensitizes cells to EGF and overrides contact-dependent inhibition of EGFR signaling (Kim and Asthagiri 2011). Increasing evidence suggests that mechanical forces elicited by the establishment of cell–cell contact are propagated across the cell cortex via cortical actomyosin (Roper 2015). For example, experimental application of force to recombinant E-cadherin-coated beads causes a global change in cellular mechanics that requires EGFR activity (Muhamed et al. 2016). Other studies reveal that cell–cell contact leads to the immobilization of EGFR across the cell cortex, and a corresponding block in EGFR internalization and signaling (Curto et al. 2007; Chiasson-MacKenzie et al. 2015). This mechanosensitive mechanism of EGFR regulation involves the functions of the neurofibromatosis type 2 (NF2) tumor suppressor, Merlin, and closely related membrane-cytoskeleton linking ERM proteins (Ezrin, Radixin, and Moesin), which configure cortical actomyosin and its interface with adherens junctions (Curto et al. 2007; Cole et al. 2008; Fehon et al. 2010; Chiasson-MacKenzie et al. 2015). Interestingly, contact-dependent immobilization of EGFR in this setting occurs within 2 minutes of EGF stimulation, requires EGFR activity and depends on medioapical actomyosin, suggesting that cells have a rapid, local mechanism for engaging activated EGFR at the plasma membrane and preventing downstream signaling in response to mechanical changes in the cell cortex (Fig. 3B) (Chiasson-MacKenzie et al. 2015).

In contrast to the inhibition of EGFR signaling in response to mechanical forces in contacting epithelial cells, contacting *endothelial* cells activate several signaling pathways in response to the mechanical forces or fluid shear imposed by blood flow (Chiu and Chien 2011). Thus mechanical forces generated by fluid shear *activate* VEGFR2 in a ligand-independent manner via a mechanism that likely involves activation of Src kinases (Tzima et al. 2005). Recent studies reveal that this mechanism requires an association between VEGFR2 and -3 with the transmembrane domain of VE-cadherin (Coon et al. 2015). In this setting the mechanosensor seems to be the platelet endothelial adhesion molecule (PECAM-1) adhesion receptor, which forms a complex with VE-cadherin and VEGFR2/3 (Tzima et al. 2005). The molecular basis of how PECAM-1 senses fluid shear and transmits that information to VEGFR2/VE-cadherin is not yet known.

ULTIMATELY AN INTERRELATIONSHIP

As suggested by many of the studies cited above, the functional interplay between RTKs and cadherin-based cell adhesion is ultimately an interrelationship. Cells within tissues undergo frequent remodeling and their exposure to both chemical and mechanical cues is constantly changing. Thus, it makes sense that they have rapid and adaptive mechanisms for dynamically coordinating the two. Two examples highlight this. First, collectively migrating cells respond to a chemokine gradient with polarized protrusive activity and ligand-induced RTK endocytic recycling at the front of the leader cell(s), which induces increased mechanical tension across cell contacts (Cai et al. 2014). At the same time, cell contacts and mechanical tension across them guide and reinforce this polarized receptor activity, distribution and turnover (Bianco et al. 2007; Prasad and Montell 2007; Cai et al. 2014). In fact, it is thought that the polarized distribution of receptors via ligand-induced receptor turnover can drive self-generated chemokine gradients in the absence of an external source (Maheshwari et al. 2001; Yu et al. 2009; Streichan et al. 2011; Scherber et al. 2012; Dona et al. 2013; Venkiteswaran et al. 2013). The sensitive balance between RTK activity and cell–cell communication provides many opportunities for tumor cells to acquire migratory, invasive behavior. Thus, cell autonomous changes in tumor cell adhesion, polarity or RTK activity, as well as nonautonomous

changes in growth factor milieu or mechanical environment evoked by adjacent tumor cells or stroma could alter the RTK:cell contact relationship and drive the invasive behavior of tumor cells.

A second example is given by the mammalian epidermis, a stratified epithelium that undergoes continuous renewal. In vivo, proliferation in the skin is restricted to the basal layer of cells where EGFR levels and activity are high (Schneider and Wolf 2008). Basal cells stop dividing and differentiate as they move apically into the suprabasal layer where EGFR activity declines substantially. It has been shown that the desmosomal cadherin desmoglein 1 (Dsg1) is required for the inhibition of EGFR activity at the suprabasal transition; thus, loss of Dsg1 leads to persistent EGFR activity and failure of these cells to differentiate (Getsios et al. 2009). In contrast, EGFR is transiently activated by keratinocyte cell–cell contact in vitro and EGFR activity is required for normal epidermal organization and function (Hansen et al. 1997). This is exemplified by the fact that whereas pharmacologic EGFR inhibitors are widely used targeted therapies in several human cancers, the key dose-limiting side-effect and predictor of treatment response is an epidermal rash that is thought to be caused in part by defective keratinocyte cell–cell communication and barrier function (Lichtenberger et al. 2013; Mascia et al. 2013; Holcmann and Sibilia 2015). Thus, too much or too little EGFR activity is detrimental to epidermal homeostasis.

Despite decades of research into the molecular basis of cell–cell communication and of RTK activation and signaling, and clear evidence of their evolutionary and functional coordination, we know surprisingly little about the dynamic interrelationship between these two critical cellular activities. This is, in part, caused by the paucity of tools with which to selectively disrupt either cell junctions or RTK activity, to dynamically monitor their coordinated activities in cells in real time and to meter the activity of each in an experimentally controlled manner. New methods of monitoring junctional dynamics and RTK trafficking by superresolution imaging combined with mechanosensors and bioengineering methods will provide an unprecedented view of this fundamental relationship.

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