Received: 24 June 2022 | Revised: 6 January 2023 | Accepted: 24 January 2023

DOI: 10.1002/wsbm.1604

ADVANCED REVIEW

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How cells sense and integrate information from different sources

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Funding information
Air Force Office of Scientific Research, Grant/Award Number: FA9550-22-1-0207; Damon Runyon Cancer Research Foundation, Grant/Award Number: DFS 38-20; Ludwig Center at MIT; Royal G. and Mae H. Westaway Family Memorial Fund; Searle Scholars Program

Edited by: Emily Frieben, Executive Editor

Abstract

Cell signaling is a fundamental cellular process that enables cells to sense and respond to information in their surroundings. At the molecular level, signaling is primarily carried out by transmembrane protein receptors that can initiate complex downstream signal transduction cascades to alter cellular behavior. In the human body, different cells can be exposed to a wide variety of environmental conditions, and cells express diverse classes of receptors capable of sensing and integrating different signals. Furthermore, different receptors and signaling pathways can crosstalk with each other to calibrate the cellular response. Crosstalk occurs through multiple mechanisms at different levels of signaling pathways. In this review, we discuss how cells sense and integrate different chemical, mechanical, and spatial signals as well as the mechanisms of crosstalk between pathways. To illustrate these concepts, we use a few well-studied signaling pathways, including receptor tyrosine kinases and integrin receptors. Finally, we discuss the implications of dysregulated cellular sensing on driving diseases such as cancer.

This article is categorized under:
Cancer > Molecular and Cellular Physiology
Metabolic Diseases > Molecular and Cellular Physiology

KEYWORDS
cell signaling, epidermal growth factor receptor, integrin, signaling crosstalk

1 | INTRODUCTION

All living organisms must be able to sense information in their environment and alter their behavior to adapt to fluctuating environmental conditions. Multicellular animals have an additional challenge—the need to coordinate numerous

Abbreviations: AKT, Ak strain transforming; CFTR, cystic fibrosis transmembrane conductance regulator; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; $GABA_AR$, gamma-aminobutyric acid Type-A receptor; GDP, guanosine diphosphate; GPCR, G protein-coupled receptors; GRB2, growth factor receptor-bound protein 2; GTP, guanosine triphosphate; HER, human epidermal growth factor receptor; HGFR, hepatocyte growth factor receptor; Ig CAM, immunoglobulin-like cell adhesion molecules; PI3K, phosphoinositide 3-kinase; RAS, rat sarcoma virus; RTK, receptor tyrosine kinase; SH2, Src homology 2; SOS, son of sevenless; TCR, T-cell receptor; TGF-α, transforming growth factor alpha.

cells across space and time (Bich et al., 2019). Comparative genomics studies between multicellular metazoans and their unicellular ancestors find that multicellular organisms evolved many distinct membrane receptors and ligands (Sebé-Pedrós et al., 2012, 2017). These receptors enable cells to coordinate and communicate information across the organism. Receiving and transmitting signals allow cells to communicate with and respond to their external environment (Azeloglu & Iyengar, 2015). Moreover, these signals are abundant and diverse, consisting of chemical, spatial, and physical information. Therefore, a cell must not only receive these signals but process and interpret them to respond appropriately to the surrounding environment.

Different receptors confer different signals and, therefore, different functions. Multicellular organisms such as humans contain hundreds of unique cell types that respond to signals differently from each other (Bianconi et al., 2013). This is in part due to the unique combination of expressed receptors, allowing for specialized cellular functions in different tissues or organs (Domanskyi et al., 2022; Marti-Solano et al., 2020). While each receptor can provide individual responses to stimuli, they often coordinate together to integrate multiple signals creating a full picture of the cellular environment (Azeloglu & Iyengar, 2015). This integration can occur through crosstalk, a commonly studied phenomenon within the signal transduction field and a focus of this review (Vert & Chory, 2011). When signaling becomes dysregulated it can lead to the onset of disease and trigger aberrant cellular behaviors (Berridge, 2013; Saraon et al., 2021; Tartaglia & Gelb, 2010; Q. Wang et al., 2019). As signaling pathways are interconnected, dysregulation of one component can have cascading effects on several others resulting in disease exacerbation and resistance to targeting therapies.

In this review, we will discuss fundamental concepts and themes underlying the current understanding of cellular signaling. We will use a few signaling pathways as examples to illustrate these concepts and discuss common mechanisms by which signaling can be disrupted in human disease. However, the concepts and signal dysregulation discussed in this review are not limited to our examples and extend across other signaling pathways and diseases.

2 | CELLS SENSE THE EXTERNAL ENVIRONMENT THROUGH SIGNALING RECEPTORS

The extracellular environment contains many different molecules such as ions, peptides, glycans, growth factors, hormones, and glycoproteins, many of which are released from other cells (Hynes & Naba, 2012). Thus, the extracellular environment is a dynamic, changing system that enables intercellular communication (Müller & Schier, 2011). Each cell in the human body is equipped to sense and respond to the diverse signals found in the extracellular space. Broadly, these signals can be categorized into chemical, spatial, and mechanical information. Chemical signals include secreted molecules that can diffuse and travel long distances, such as growth factors and hormones (Müller & Schier, 2011). Chemical signals can transmit information rapidly and enable communication between cells over long distances. Spatial signals like basement membrane molecules enable cells to orient themselves within their environment and provide the basis for the organization of cells into tissues (Sekiguchi & Yamada, 2018). Mechanical signals include the stiffness of the environment and the forces generated within tissues, such as the shear force of blood passing through vessels (Chanet & Martin, 2014). These mechanical signals provide important information about the local microenvironment.

To sense the diverse signals present in the extracellular environment, cells rely on various protein receptors embedded in the plasma membrane. The main types of receptors in human cells include channel-linked receptors, enzyme-linked receptors, G protein-coupled receptors (GPCRs), and adhesion receptors (Figure 1). Channel-linked receptors allow ions and other lipid membrane-impermeable molecules to exchange between cells and environment (Li et al., 2014). Many of these channels, such as gamma-aminobutyric acid Type-A receptor ($GABA_AR$), require binding to ligands such as neurotransmitters to open or close the channel (Ghit et al., 2021). Enzyme-linked receptors are activated by an extracellular signal and become enzymatically active primarily by an intracellular kinase domain, phosphatase domain, or guanylyl cyclase domain (Lemmon & Schlessinger, 2010). GPCRs are seven-pass transmembrane receptors that act as guanine nucleotide exchange factors (GEFs) to activate and release intracellular G proteins upon ligand binding (Rosenbaum et al., 2009; Seyedabadi et al., 2022). A single GPCR can activate many G proteins to rapidly amplify the signal (Ross, 1989). Finally, adhesion receptors physically link the extracellular environment to intracellular cytoskeletal proteins (Kim et al., 2011). These receptors include cell–cell linking cadherins, cell-matrix coupling integrins, cell adhesion immunoglobulin-like cell adhesion molecules (Ig CAMs), and sugar-binding selectins commonly involved in immune cell arrest from circulation (Harjunpää et al., 2019; Patel et al., 2003). Each of these different classes of receptors can recognize specific extracellular signals and initiate a specific intracellular response. Moreover,

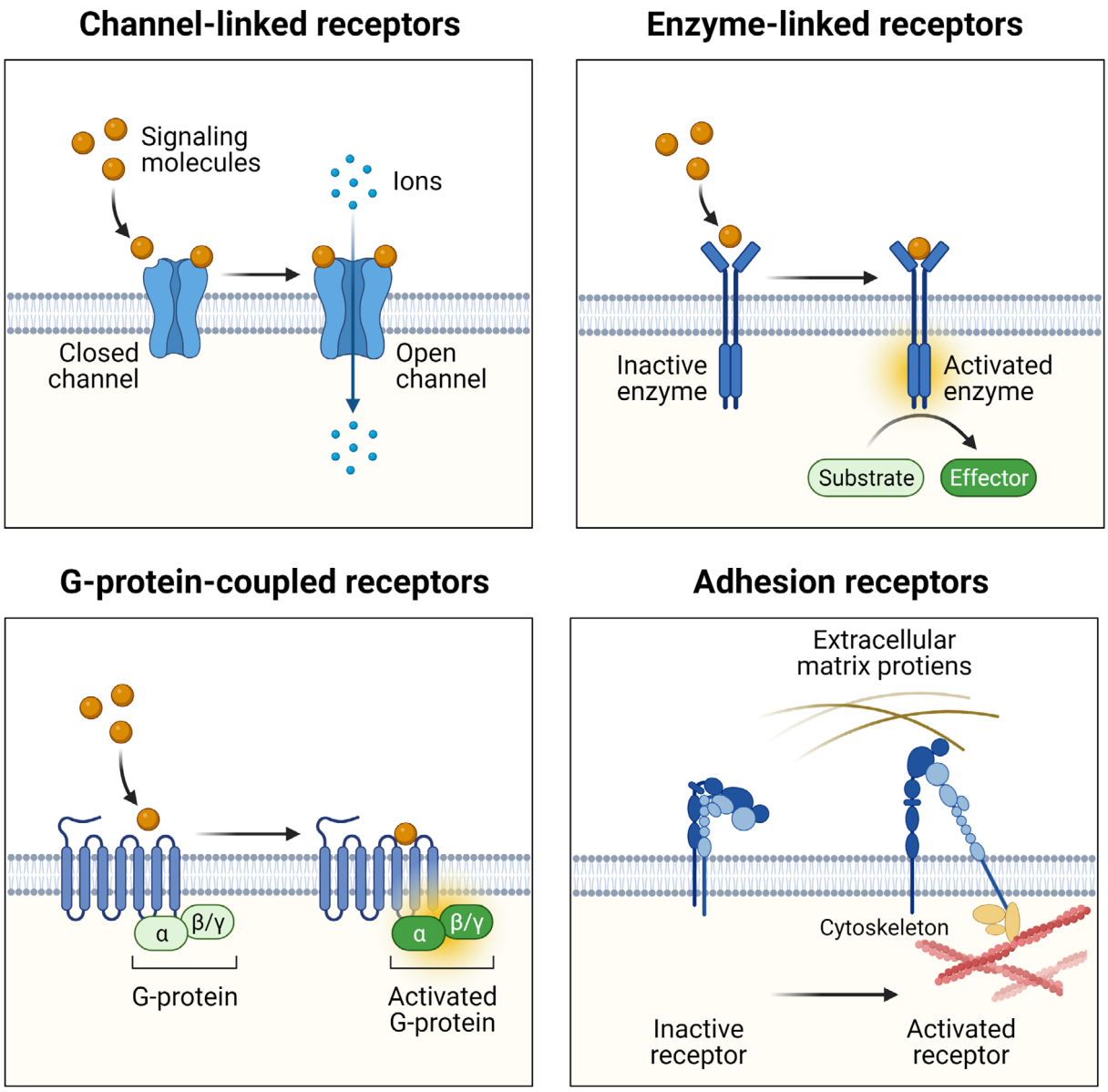

FIGURE 1 Types of signaling receptors. Channel-linked receptors can sense and transport ions across the membrane (*top*, *left*). Enzyme-linked receptors such as receptor tyrosine kinases can activate the enzymatic domain upon ligand binding (*top*, *right*). G protein-coupled receptors bind to ligands including neurotransmitters, odorants, photons, and hormones triggering activated G protein release and downstream signaling (*bottom*, *left*). Adhesion receptors bind to the extracellular matrix and physically link the outside to the intracellular cytoskeleton (*bottom*, *right*). *Created with Biorender*.

sharing of ligand between receptors is common and crosstalk between pathways can lead to complex outputs. Typically, binding of a receptor to its cognate ligand leads to a conformational change in protein structure. This can have different effects on the receptor, such as promoting receptor oligomerization, activating a receptor's enzymatic activity, revealing adaptor protein binding domains, or opening a channel for ion exchange (Figure 1). In turn, this elicits signaling pathway activation and therefore cellular response. The signaling pathway emanating from a single receptor is often a complex network with intricate layers of regulation resulting in the modification of multiple downstream targets.

Human cells can contain many different receptors (100s–1000s of receptors, depending on the cell type) embedded within a densely packed plasma membrane (typically ~30,000 molecules/micron^2) (Jacobson et al., 2007, 2019; Quinn et al., 1984). The combination of expressed receptors on a cell's surface dictates the specific signals that can be sensed. There is also overlap between different signaling pathways with common adaptor proteins, enzymes, and downstream targets shared between different pathways. For instance, humans have 58 receptor tyrosine kinases (RTKs) that can

elicit unique cell proliferative responses to different ligands despite using overlapping adaptor proteins and downstream targets (Lemmon & Schlessinger, 2010; Vasudevan et al., 2015). The same receptor can also elicit different cellular responses depending on the context. For example, activation of epidermal growth factor receptor (EGFR) by different ligands such as epiregulin or epidermal growth factor (EGF) can result in either differentiation or proliferation responses, respectively (Freed et al., 2017). Thus, cells must be able to simultaneously sense many different signals and integrate this information to achieve the appropriate cellular response. Within the context of a cell's complex microenvironment, multiple receptors are being activated by multiple ligands leading to simultaneous pathway activation (Kim et al., 2011). How cells integrate this information remains an exciting area of ongoing research.

Appropriate receptor signaling is critical for healthy cell function. Disease can be triggered when components of signaling pathways become dysregulated by altered expression, mutations, or other mechanisms. The dysregulation of the same receptor can trigger a diversity of disease presentations depending on the cell type and tissue context. For instance, downregulation of the RTK hepatocyte growth factor receptor (HGFR) is associated with increased risk of autism spectrum disorder (D. B. Campbell et al., 2006), while HGFR is hyperactivated in various cancers including non-small cell lung cancer, papillary renal carcinoma, and other adenocarcinomas (Ma et al., 2005; Schmidt et al., 1997). Additionally, abnormal receptor function affects distinct organs and tissues differently. Within the respiratory epithelia, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) ligand-gated ion channel lead to impaired membrane targeting of the receptor or impaired chloride ion shuttling (Cheng et al., 1990; Riordan et al., 1989; Yeh et al., 2019). This, in turn, causes water retention within lung epithelial cells leading to mucus build-up and airway obstruction—hallmark consequences of the genetic disorder cystic fibrosis (Boucher, 2002). Moreover, CFTR dysfunction is not limited to respiratory tissue but also impacts other tissues and organs such as the intestine, pancreas, sweat glands, and reproductive system. In the pancreas, CFTR is important for exocrine secretion and its mutation can lead to impaired secretion of sodium bicarbonate and water in cystic fibrosis patients (Ishiguro et al., 2009; Lee et al., 2012). In addition to being commonly dysregulated in disease, receptors are also localized on the surface of the cell and easily accessible to small molecules and antibodies (Imai & Takaoka, 2006; Yin & Flynn, 2016). Therefore, they are common candidates for pharmacological intervention in human disease.

3 | CHEMICAL COMMUNICATION DELIVERS RAPID INFORMATION

Chemical cues provide a mechanism for rapid signal diffusion between cells and throughout an organism. These cues include secreted peptides, hormones, neurotransmitters, ions, and growth factors (Müller & Schier, 2011). Cell membranes are embedded with a multitude of protein receptors that recognize specific chemical ligands and initiate an intracellular response (Jacobson et al., 2019).

One mechanism to couple ligand binding to an intracellular response is via direct interactions between a ligand-sensing receptor and an intracellular enzymatic molecule. For example, GPCRs have an extracellular domain that recognizes ions, odorants, photons, hormones, vitamins, or neurotransmitters and an intracellular domain that binds directly to G proteins, enzymes that cycle between guanosine diphosphate (GDP) and guanosine triphosphate (GTP; Chen et al., 2022; Hilger et al., 2018). Upon GPCR ligand binding, GDP is exchanged for GTP, and G proteins are released from the receptor which triggers enzyme activity. GPCRs elicit rapid cellular responses to light, odors, peptides, and neurotransmitters (Chen et al., 2022; Hilger et al., 2018).

Growth factors are chemical signals that regulate cell proliferation, help maintain tissue homeostasis, and regulate metabolism. Growth factors can signal in either autocrine (self-released signal), paracrine (neighbor-released signal), or endocrine (circulation-released signal) methods. Many growth factors bind to RTKs, a family of receptors that typically contain an extracellular ligand-binding domain and an intracellular kinase domain (Lemmon & Schlessinger, 2010). By combining ligand binding and enzymatic activity within a single molecule, RTKs can efficiently recognize the extracellular signal and self-activate to transduce the information intracellularly. For instance, EGF is a cleaved and secreted ligand capable of binding and acting on the RTK EGFR in an autocrine, paracrine, or endocrine fashion. Ligand binding drives conformational changes to reveal the dimerization arm of the ligand-bound receptor (Garrett et al., 2002). This drives dimerization of the extracellular domains of two EGFR molecules and leads to subsequent activation of its intracellular kinase domains (Figure 2). The EGFR family of receptors consists of structurally similar members EGFR/HER1 (human epidermal growth factor receptor 1), EGFR2 (HER2), EGFR3 (HER3), and EGFR4 (HER4). Some RTKs lack either ligand-binding or kinase activity. However, these receptors are still capable of robust signaling partly due to their ability to heterodimerize with other functional RTK family members (Littlefield et al., 2014). For example, HER2,

a RTK incapable of ligand binding, and HER3, a RTK with weakened kinase activity, can form a signaling-competent heterodimer (Wallasch et al., 1995). Additionally, EGFR and HER2 have recently been shown to homo- and hetero-dimerize in the absence of ligands and become activated, but the consequences of this ligand-free activation remain unclear (Byrne et al., 2020).

3.1 | Adaptor proteins coordinate receptor signaling to different pathways

Activated receptors often bind and recruit other proteins to the membrane to form supramolecular signaling clusters that can range from nanometers to micrometers in diameter (Jacobson et al., 2019; Mayer & Yu, 2018; Figure 2). Receptor activation can expose binding sites for intracellular proteins through conformational changes or post-translational modifications. For example, phosphorylation of tyrosine residues within the RTK cytoplasmic domain creates binding sites for Src homology 2 (SH2) domain-containing proteins (Kaneko et al., 2012). Adaptor, scaffold, and docking

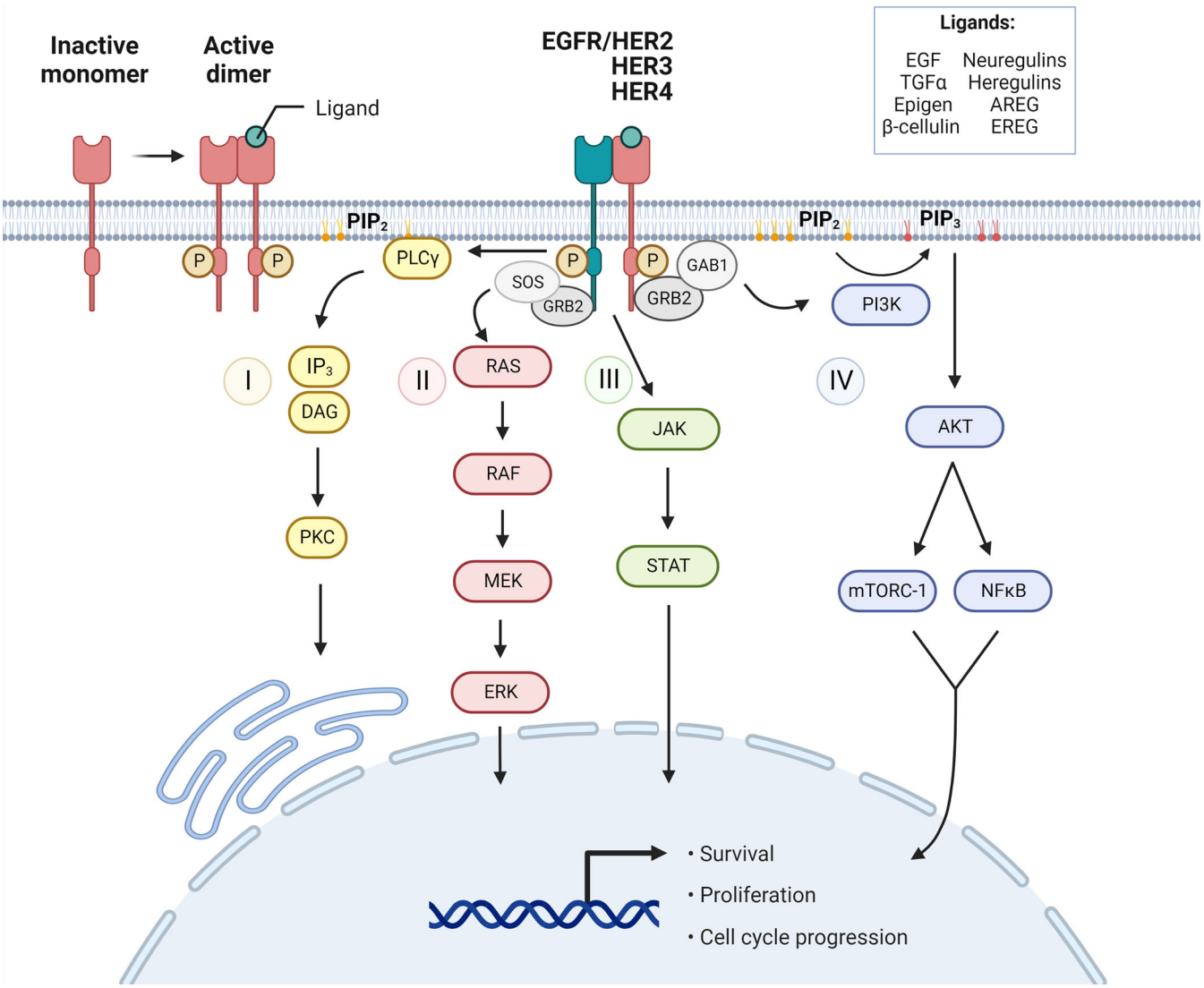

FIGURE 2 EGFR-family receptor signaling at a glance. Upon ligand binding to the extracellular domains, monomeric EGFR dimerizes with itself or other EGFR-family members including HER2, HER3, and HER4. This initiates kinase activity and autophosphorylation of tyrosines on the C-terminal tail. Adaptor proteins bind and recruit signal transduction complexes. Activation of PKC through direct binding of PLCγ (I), the MAPK pathway through Grb2/SOS recruitment (II), the JAK/STAT pathway through direct receptor binding (III), and the PI3K/AKT pathway through Grb2/Gab1 association (IV) influences gene expression to alter cell survival, proliferation, differentiation, and cell-cycle progression. *Created with* Biorender.com.

proteins interact with activated receptors depending on the compatibility of binding sites available. These recruited intracellular proteins function together to coordinate the specific activation of downstream pathways and ultimately a cellular action.

The recruitment and coordination of intracellular proteins are critical for RTK signaling. For example, the clustering of EGFR results in robust activation of multiple downstream signaling pathways including mitogen-activated protein kinases (MAPK) and phosphoinositide 3-kinase (PI3K)/Ak strain transforming (Akt) signaling (Egan et al., 1993; Humtsoe & Kramer, 2010). To coordinate the proper signal transduction pathway, combinations of adaptor proteins will localize and bind to activated receptors (Bongartz et al., 2019). Different adaptor proteins are responsible for the activation of MAPK signaling and PI3K/Akt signaling. Growth factor receptor-bound protein 2 (Grb2) binds directly to the phosphotyrosines on the C-terminal tails of many RTKs, including EGFR. Grb2 then recruits son of sevenless (SOS) which can activate rat sarcoma virus (Ras) small GTPase at the membrane to trigger the MAPK signaling cascade (Egan et al., 1993; McCormick, 1993). While both MAPK and PI3K signaling leads to cell growth and survival, their differential activation can also promote unique outcomes. This is largely due to the presence and timing of adaptor protein recruitment (Ronan et al., 2016). Interestingly, different receptors can compete for adaptor protein binding to influence signaling outcomes. For instance, EGF/EGFR can outcompete ephrin-A1/EphA2 receptors for Grb2 and SOS binding (Oh et al., 2022). Accordingly, the recruitment of adaptor proteins to different receptors could shift their downstream effectors and change the cellular response.

3.2 | Ligand properties influence downstream signaling

Single receptors often bind many types of ligand, and the binding of different ligands can elicit unique responses. This not only allows for receptors to be activated by multiple types of chemicals, but also allows the same receptor machinery to activate different downstream signaling cascades. For example, low-affinity ligand (epiregulin and epigen) binding to EGFR results in weaker receptor dimerization when compared to high-affinity ligand (EGF; Freed et al., 2017). As a result, epiregulin and epigen lead to sustained extracellular signal-regulated kinase (Erk) activation whereas EGF leads to transient Erk activation (Freed et al., 2017). Specific ligand-induced conformations can influence downstream signaling. EGF and transforming growth factor alpha (TGF-α) both bind EGFR with similar affinities (Jones et al., 1999). However, EGF and TGF-α create different extracellular dimer conformations which propagate distinct intracellular kinase activities with each bound ligand (Y. Huang et al., 2021). Moreover, ligands can bias the formation of specific heterodimer combinations (Macdonald-Obermann & Pike, 2014). For example, betacellulin binding influences EGFR to preferentially form heterodimers with HER3 (Rush et al., 2018). Finally, ligand concentration can modulate the receptor response and endocytosis. Low EGF stimulation increases EGFR recycling while high EGF directs EGFR toward degradation (Sigismund et al., 2008). Thus, the identity, affinity, and concentration of available ligands influences downstream signaling.

Different ligands can also preferentially activate one signaling response over another downstream of a receptor, a phenomenon termed biased agonism or functional selectivity (Wootten et al., 2018). Biased agonism can occur when ligands preferentially stabilize different conformational states of the same receptor, leading to distinct cellular responses. Identifying biased agonists for different receptors, especially GPCRs, is ongoing in the signaling and drug discovery fields (Michel & Charlton, 2018). For example, biased agonists of the GPCR μ opioid receptor have been successful in treating pain with less negative side effects during phase II clinical trials (Viscusi et al., 2016). Identifying and understanding the mechanism of biased agonists for other receptors such as RTKs could create new avenues for disease treatment.

3.3 | Chemical signaling dysfunction in disease

In healthy cells, chemical communication is regulated, but dysregulation of receptors can cause diseases such as cancers, autoimmune disorders, and skeletal dysplasias (McDonell et al., 2015; Saraon et al., 2021; Wu et al., 2018). In many cancers, EGFR and HER2 are frequently hyperactivated as a result of genetic alterations (Berger et al., 1988; Shigematsu & Gazdar, 2006; Slamon et al., 1987). Specifically, point mutations and exon deletions can constitutively activate the EGFR kinase domain leading to hyperphosphorylation, common in nonsmall cell lung cancer (Lynch et al., 2004). Gene amplifications of HER2 result in receptor overexpression in adenocarcinomas, breast, and other

cancers (Gordon et al., 2013; Press et al., 1997). Dysregulated EGFR localization can lead to the formation of large, punctate EGFR aggregates at the membrane (Y. Wang et al., 2014). Many of these changes create an EGFR capable of signaling in the absence of ligand (Valley et al., 2015). Consequently, the EGFR pathway constitutively stimulates cell proliferation and survival, leading to increased tumorigenesis and cancer progression.

4 | CELL ADHESION DELIVERS SPATIAL INFORMATION

The local tissue microenvironment consists of different cell types as well as secreted extracellular matrix (ECM) molecules (Karamanos et al., 2021). Adhesion receptors provide cells with information about their spatial context within the tissue by recognizing specific receptors on other cells or specific molecules in the ECM. Immunoglobulin domain-containing receptors, cadherins, and selectins are receptors that mediate adhesion between two cells, while integrins, hyaluronan receptors, and sarcoglycans are receptors that mediate adhesion with the extracellular matrix (Juliano, 2002; Karamanos et al., 2021; Tarakci & Berger, 2016). These cell adhesion receptors enable cells to acquire information about the microenvironment including the types of neighboring cells and the local ECM composition. Cell adhesion receptors often directly or indirectly connect to the internal cytoskeleton, serving as an anchor to the external environment and helping to physically integrate the tissue. Cell adhesion receptors can also initiate signaling cascades, often through the recruitment and activation of kinases and Rho GTPases, to regulate cell survival, metabolism, cell cycle progression, cell migration, and differentiation (Juliano, 2002).

Integrins are heterodimers composed of an α and β subunit, and eight β subunits can combine with 18 α subunits to form 24 distinct integrin heterodimers in humans (Hynes, 2002). The large ectodomain domain of integrins determines ligand specificity and the intracellular domains bind to cytoplasmic adaptor proteins (I. D. Campbell & Humphries, 2011; Z. Sun et al., 2019). Similar to RTKs, integrin heterodimers undergo complex conformational changes during their activation and adopt several distinct conformations (Chastney et al., 2021; Luo et al., 2007; Springer & Dustin, 2012; Takagi et al., 2002; Wen et al., 2022).

4.1 | Adaptor proteins coordinate receptor signaling to different pathways

Unlike RTKs, cell adhesion receptors contain no intrinsic catalytic activity, and downstream signaling is dependent upon the assembly of receptors with cytoplasmic adaptor proteins and signaling molecules (Chastney et al., 2021). For example, upon activation integrins undergo clustering and supramolecular assembly to form micron-sized integrin adhesion complexes, such as focal adhesions (Case & Waterman, 2015), podosomes (Weber et al., 2022), hemidesmosomes (te Molder et al., 2021), and costameres (Cutroneo et al., 2012). The composition and morphology of integrin complexes can vary depending on the cell type and physiological context.

Integrins primarily signal through cytoplasmic tyrosine kinases and Rho-family GTPases. Focal adhesion kinase (FAK) and c-Src are non-RTKs that phosphorylate substrates downstream of integrin activation (Chastney et al., 2021). FAK is targeted to focal adhesions via its C-terminal domain (Hildebrand et al., 1993). After focal adhesion localization, FAK undergoes autophosphorylation to create a high-affinity binding site for the SH2 domain of Src family kinases (Schlaepfer et al., 1999; Tapial Martínez et al., 2020). Together, the FAK-Src complex phosphorylates multiple substrates including paxillin and p130Cas (Roy et al., 2002). Activation of the FAK-Src complex can lead to downstream activation of PI3K/Akt and Erk/MAPK pathways (Schlaepfer et al., 1999).

Cell adhesion receptors also signal through the recruitment and activation of Rho-family GTPases, molecular switches that are activated through the binding of GTP and inactivated by GTP hydrolysis (Parri & Chiarugi, 2010). GEFs catalyze the exchange of GDP to GTP to activate the GTPase activity. Integrin adhesion complexes can recruit specific GEFs to activate either Rho, Rac, or Cdc42 GTPases. βPix is a GEF for Rac1 and is localized within newly formed focal adhesions to promote protrusion and focal adhesion turnover (Kuo et al., 2011). In contrast, the Rho GEFs LARG and GEF-H1 are recruited to growing focal adhesions to promote cytoskeletal remodeling (Guilluy et al., 2014).

Recruitment of adaptor proteins to adhesion receptors can also inhibit signaling. For example, filamin binds to the cytoplasmic domain of integrin, maintaining integrin in an inactive conformation (Liu et al., 2015). Thus, filamin binding inhibits integrins and decreases cell migration (Calderwood et al., 2001).

4.2 | Receptors can signal bidirectionally across the plasma membrane

Transmembrane receptors often gather information from the external environment to induce changes in intracellular behavior. However, intracellular information can also be propagated through receptors to the extracellular space, which can facilitate communication between cells. Integrins are a well-studied example of receptors that signal bidirectionally across the plasma membrane (Hynes, 2002; Minsoo et al., 2003; Wen et al., 2022). The high affinity, active conformation of integrin can be favored by the binding of cytoplasmic proteins, such as talin, to the β-integrin tail ("inside-out" activation) or by the binding of the integrin ectodomain to extracellular ligand ("outside-in" activation; Takagi et al., 2002). Thus, both internal and external signals can initiate integrin activation.

4.3 | Cell adhesion dysfunction in disease

Since cell adhesion receptors are essential for the proper formation and function of all tissues and organs, dysregulated cell adhesion is a common cause for many human diseases. Dysregulated cell adhesion in the immune system can lead to leukocyte adhesion deficiency, chronic inflammation, and autoimmune disorders (Dustin, 2019). Impaired cell–cell adhesion can disrupt epithelial barriers and contribute to blistering disease and inflammatory bowel disease (Hammers & Stanley, 2016; Marchiando et al., 2010). Many pathogens, including *Vibrio cholerae* and *Escherichia coli*, disrupt cell–cell adhesion in the intestinal epithelia causing severe gastrointestinal symptoms (Marchiando et al., 2010). The dysregulation of cell adhesion is also common in many cancers (Dustin, 2019). The epithelial-to-mesenchymal transition (EMT) occurs when epithelial tissues lose apical-basal polarity and organized cell–cell adhesion, and EMT is a common step in cancer progression (Aiello & Kang, 2019). During EMT, solid tumors become more malignant and metastatic, and preventing EMT is one strategy for treating drug-resistant cancers (Shibue & Weinberg, 2017).

5 | CELLS SENSE AND RESPOND TO MECHANICAL INFORMATION

Mechanical forces and the material properties of the environment have profound effects on animals at the whole organism, organ, tissue, and cellular levels, including the behavior of individual cells during development, differentiation, and adult physiology. At the tissue and organ level, lungs expand and contract stretching the epithelial tissue, the heart pumps blood creating shear stress against endothelial cells, and increased weight-bearing during physical activity stimulates bone remodeling (Ramkhelawon et al., 2009). At the cellular level, the stiffness and surface topology of a stem cell's environment can direct its differentiation and control the fates of its progeny (Vining & Mooney, 2017). Mechanotransduction is the molecular process by which cells sense and respond to mechanical signals in their environment. Cells use many pathways to sense mechanical information. Mechanosensitive ion channels, such as Piezo1, change conformation in response to mechanical stimuli to initiate Ca^{2+}-dependent signaling cascades (Coste et al., 2010). Several GPCRs can also be activated by mechanical stretch. For example, mechanical stretch is sufficient to activate angiotensin II type 1 receptors (AT1R), leading to G protein release, ERK activation, and cardiac hypertrophy (Zou et al., 2004). Mechanical forces can also be directly transmitted across adhesion receptors, such as integrins and cadherins, promoting the recruitment of intracellular molecules to adhesion complexes (Case & Waterman, 2015). For example, the composition of focal adhesions changes dramatically in response to increased mechanical forces, and integrin-dependent signaling is sensitive to mechanical cues such as substrate stiffness and actomyosin contractility (Schiller et al., 2013). Mechanical forces can also be sensed directly by the cytoskeleton. The actin filament helical structure changes under tension, and many proteins recognize and bind specifically to tensed actin filaments (Mei et al., 2020; Sakao & Tatsumi, 2011; X. Sun et al., 2020). Changes in actin filament tension can also be relayed through the transcription factors Yap/Taz to promote cell proliferation (Dupont et al., 2011). A variety of external mechanical signals, such as shear stress, stretch, cell–cell contact, and ECM stiffness, cause actin cytoskeleton remodeling, leading to dephosphorylation and nuclear translocation of Yap/Taz to activate transcription (Dupont et al., 2011; Wada et al., 2011). External forces can influence microtubules and can dictate the position and orientation of the mitotic spindle (Brangwynne et al., 2007; Fink et al., 2011). The cytoskeleton is also physically connected to the nuclear lamins by the linker of nucleoskeleton and cytoskeleton (LINC) complex, allowing external mechanical forces to be propagated to the nucleus to regulate chromosome organization and transcription (Uhler & Shivashankar, 2017). Moreover, the LINC complex feeds back into regulating overall cellular mechanics by altering actin dynamics through Rho GTPase activity

(Thakar et al., 2017). Altogether, the cell contains many avenues to sense and be influenced by the surrounding mechanical environment—a critical component for spatially complex multicellular organisms.

5.1 | Forces can directly alter the conformation of proteins

At the molecular level, proteins convert force into biochemical activity by undergoing force-dependent conformational changes which can create new binding sites, alter binding affinity, or directly change molecular activity. Mechanical stretching of the focal adhesion adaptor protein talin unfolds rod domains to reveal "cryptic" binding sites for the protein vinculin (del Rio et al., 2009). Talin contains 13 rod domains that reversibly unfold under different magnitudes of force, leading to mechanosensitive recruitment of vinculin to focal adhesions (Yao et al., 2016). At adherens junctions, the adaptor protein αE-catenin connects cadherin receptors to the actin cytoskeleton, and the cadherin-actin interaction strengthens with increasing force due to a force-induced conformational change in the αE-catenin actin-binding domain (Buckley et al., 2014; A. Wang et al., 2022). Membrane tension is sufficient to induce a conformational change in Piezo1 that activates its ion channel activity (Lin et al., 2019; Syeda et al., 2016).

5.2 | Mechanotransduction in disease

Abnormal mechanotransduction contributes to many human diseases including asthma, heart failure, osteoporosis, and cancer (Ingber, 2003). In disease, changes in mechanotransduction are often coupled with complex changes in chemical or spatial signal transduction. Disrupted mechanotransduction can lead to different symptoms depending on the tissue context. Mutations in mechanosensitive Piezo channels can lead to diseases such as lymphatic dysplasia, anemia, muscular atrophy, and cardiovascular disease (Alper, 2017). Dysregulated integrin-dependent mechanotransduction contributes to the progression of diseases such as osteoporosis and cancer (Z. Sun et al., 2016). Dysregulated mechanotransduction in sensory hair cells is a common cause of deafness (Caprara & Peng, 2022).

6 | CROSSTALK: MERGING SIGNALS TO DEVELOP A FULL PICTURE OF THE SURROUNDING ENVIRONMENT

Signaling crosstalk occurs when one pathway's activity tunes that of another. Signaling crosstalk is prevalent in human cells, and crosstalk has enabled multicellular organisms to develop specialized cell types and organ systems that rely on intercellular communication (Rowland et al., 2017). Rather than evolve a new signaling pathway de novo, different cell types can use the same receptors and signaling pathways to achieve unique outcomes. In response to EGFR activation, keratinocytes will activate pro-survival pathways upon UV damage, whereas hepatocytes induce proliferation and liver regeneration upon injury (Natarajan et al., 2007; Peus et al., 2000). Each cell type expresses a unique combination of receptors and exists within a specific microenvironment, and cross-talk enables these differences to influence signaling. Crosstalk is a broad term defined by the interdependence of two signaling pathways. Although crosstalk is frequently observed across all forms of signaling, it is not always well understood at a molecular level. Integrin and EGFR crosstalk has been extensively studied and provides insight into some of the distinct molecular mechanisms that can drive signaling crosstalk shared across all pathways (Figure 3). Additionally, crosstalk occurs between a variety of receptor types including GPCRs and other RTKs. These relationships have been reviewed elsewhere (Di Liberto et al., 2019; Kilpatrick & Hill, 2021; Z. Wang, 2016). However, we highlight a few examples below to illustrate general crosstalk mechanisms.

6.1 | Shared ligand binding

Many receptors are capable of binding to multiple ligands in the extracellular space with varying affinities. In other words, cells do not always evolve a unique receptor for every existing ligand. One mechanism by which pathway A can influence pathway B is by the binding of both receptors to the same ligand. Several types of integrins can also bind to

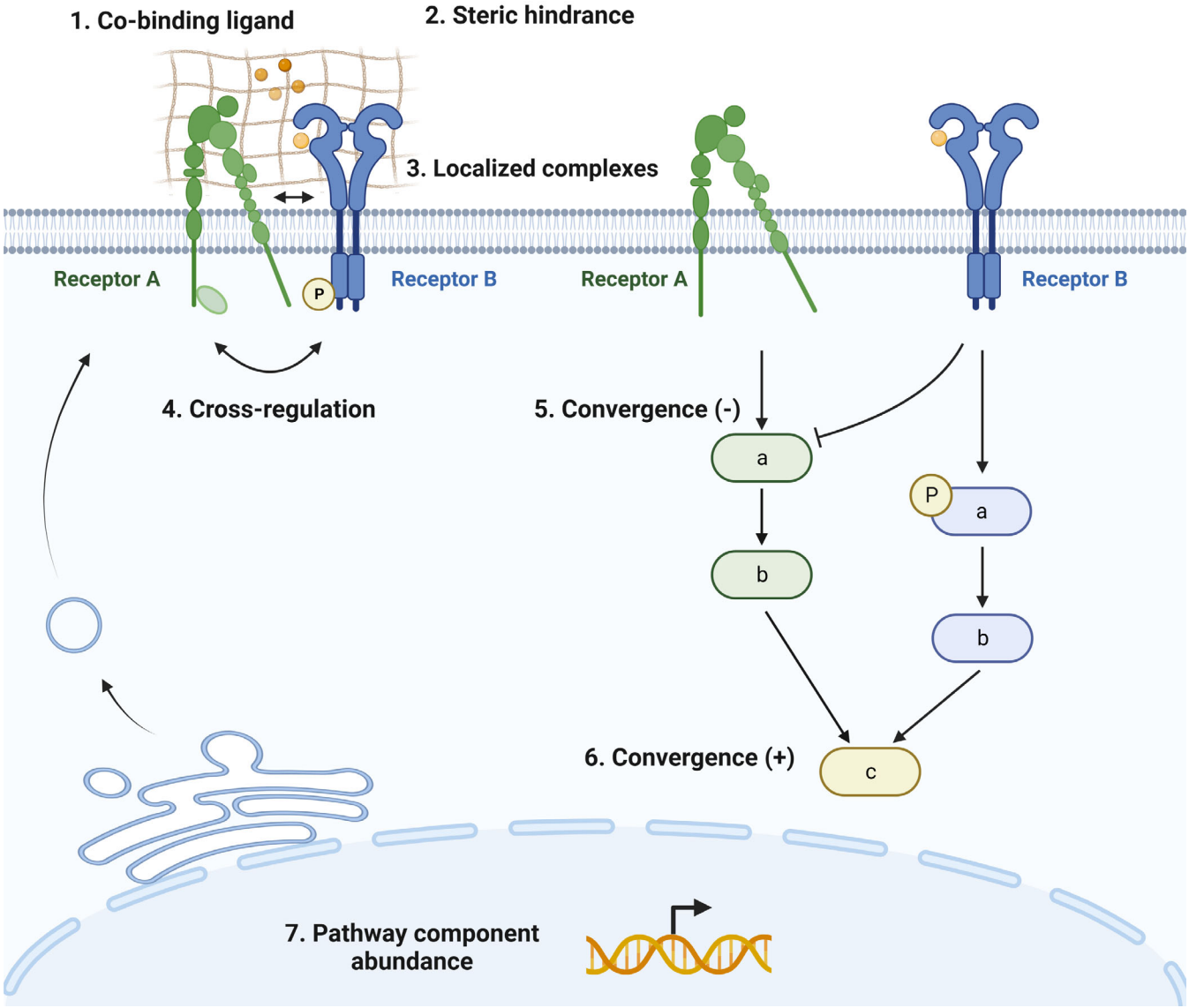

FIGURE 3 Conceptual mechanisms of crosstalk between signaling pathways. These include shared/co-binding ligand (1), steric hindrance (not illustrated) (2), localized receptor complexes (3), cross-regulation (4), converging on the same downstream target through negative convergence (5) or positive convergence (6), and pathway component availability through transcription/translation, recycling, and degradation (7). *Created with* Biorender.com.

different growth factors (Munger et al., 1999; Saegusa et al., 2009). For example, integrin $\alpha_v\beta_3$ binding to the ligand FGF is important for propagating FGF signaling in promoting DNA synthesis and cell proliferation (Mori et al., 2008). GPCRs from the same GPCR families and, less frequently, different families can bind the same ligands due to similar structure and electrostatic properties of the ligand binding pockets (Dankwah et al., 2022). Not only does a receptor binding to a different ligand propagate different responses, but it can also create competition between receptors for a finite pool of ligands (Antebi et al., 2017; Szilágyi et al., 2022).

6.2 | Steric hindrance

The spatial separation of receptors into distinct regions of the membrane can influence their signaling and crosstalk. Large and bulky receptors can impose steric restraints on the size of molecules that can easily access certain receptor clusters. For example, bulky glycoproteins sterically restrict integrin–ECM interactions, leading to increased integrin

clustering and focal adhesion assembly through a physical kinetic trap (Paszek et al., 2009, 2014). Therefore, the upregulated expression of bulky glycoproteins in metastatic human tumor cells leads to an increase in integrin adhesion and signaling (Paszek et al., 2014). In T-cells, the receptor protein tyrosine phosphatases CD45 and CD148 have large, bulky extracellular domains, while the T-cell receptor (TCR) has a small extracellular domain. Thus, CD45 is excluded from TCR microclusters, leading to increased phosphorylation of the TCR and downstream activation of Lck kinase (Choudhuri et al., 2005; Irles et al., 2003). In mast cells, the large cytoplasmic domain of clustered immunoglobulin E-receptors (FcεRI) can reduce the recruitment of cytoplasmic PTPα phosphatase to suppress dephosphorylation of the receptor (Nirmalya et al., 2021). Thus, steric limitations imposed by both the extracellular and intracellular domains of receptors can potentially influence crosstalk and downstream signaling.

6.3 | Localized complexes

Another mechanism of signaling crosstalk is through the localization of two different receptors within the same region of the membrane. Receptor A can recruit receptor B to activate it, sequester it, or expose it to an alternative pool of adaptor proteins. Thus, recruitment of receptors to distinct membrane locations can create unique signaling platforms. Localized receptors can be physically linked through hetero-oligomerization or be sequestered in the same membrane domain. The proximity of two different receptors can influence their respective activation, adaptor protein recruitment, and signaling outcomes. Receptors can co-localize through direct, physical interactions between receptor A and receptor B. For example, the GPCR adenosine A_{2A} receptor and FGFR directly interact via their intracellular domains. When these two receptors associate, co-activation of both receptors, but not individual activation of either receptor alone, activates the MAPK pathway to trigger differentiation and morphogenesis in neuronal cells (Flajolet et al., 2008). Receptors can also co-localize through direct interactions with downstream adaptor proteins. For example, EGFR and integrins can complex together through FAK–EGFR interactions (Moro et al., 2002; Sieg et al., 2000; Tice et al., 1999). These interactions can create different consequences for focal adhesion dynamics and shift cell mechanics from adhesive to contractile (Chan et al., 2021). Membrane sub-domains can influence receptor location and interactions (Duncan et al., 2020; Hang et al., 2015; Mineo et al., 1996; Pike, 2003). For example, EGF stimulation leads to changes in clathrin lattice organization at the plasma membrane, which leads to sequestration of EGFR and β5-integrin into a signaling scaffold (Alfonzo-Méndez et al., 2022).

Clustering of receptors may also function as a crosstalk mechanism to couple and tune cellular response to mechanical stimuli. The E-cadherin receptor CDH1 and EGFR form a complex consisting of two E-cadherins and one EGFR (Brendan et al., 2022). EGFR signaling becomes connected to mechanical tension through E-cadherin, where increased tension disrupts the heteroreceptor connection and releases EGFR to become activated and signal (Brendan et al., 2022).

6.4 | Cross-regulation

Another mechanism of crosstalk between different pathways is through cross-regulation, whereby components of pathway A can positively or negatively impact pathway B through physically binding or modifying components. For example, activated kinases of one pathway can phosphorylate residues of another. Activated $\alpha_v\beta_3$ and β_1 integrin triggers c-Src to phosphorylate EGFR (Moro et al., 2002). This has been proposed to alter EGFR signaling in the absence of EGF ligand through lateral signal propagation (Kansra et al., 2005; Shan et al., 2012). Furthermore, cross-regulation can also be observed downstream of receptors. EGFR signaling through Erk and Rho can lead to activation of filamin A to maintain integrin in an inactive conformation and inhibit integrin signaling (Vial & McKeown-Longo, 2012). EGF-mediated EGFR activation also increases integrin tension during cell spreading and promotes focal adhesion maturation potentially through RhoA and Rac1 activation (Rao et al., 2020). In vascular smooth muscle cells, the ligand Angiotensin II binds the GPCR AT1R, triggering NADPH oxidase-dependent generation of reactive oxygen species (ROS; Frank et al., 2001). This leads to an increase in EGFR phosphorylation and downstream ERK activation, likely through ROS-dependent inhibition of phosphatase activity.

6.5 | Convergence on downstream targets

Independent receptors and the pathways they activate can converge on shared downstream targets. Convergence can be positive (i.e., coherent feed-forward) or negative (i.e., incoherent feed-forward). In positive convergence,

pathways A and B both act on the same downstream target resulting in an additive response. In negative convergence, pathways A and B act on the same downstream target creating an antagonistic response through competition. Several GPCRs and RTKs can positively converge to activate shared downstream targets such as the PI3K and MAPK pathways (Blaukat et al., 2000; Dizeyi et al., 2011; Suire et al., 2012). For example, serotonin binding to GPCRs in endothelial cells can activate PI3K/Akt signaling to a similar extent as VEGF binding to the VEGFR (Zamani & Qu, 2012).

Positive convergence also occurs between integrin and EGFR signaling pathways. When FAK and EGFR associate with the same downstream adaptor proteins Grb2 and SOS, they can synergistically activate MAPK and Erk (Miyamoto et al., 1996; Schlaepfer et al., 1994). Conversely, EGFR and integrins have the potential to negatively converge on phosphoinositide signaling. EGFR activates PI3K which phosphorylates and converts phosphatidylinositol(4,5) bisphosphate ($PI(4,5)P_2$) to phosphatidylinositol(3,4,5)trisphosphate ($PI(3,4,5)P_3$) (Czech, 2000; Kiyatkin et al., 2006). However, FAK activates phosphatase and tensin homolog (PTEN) which dephosphorylates ($PI(3,4,5)P_3$) to generate PIP_2 (Tzenaki et al., 2015). Whether these two pathways result in negative convergence on the downstream phosphoinositide targets remains unexplored.

6.6 | Pathway component availability

Finally, a mechanism by which one pathway can influence another is through regulating the availability of their components. Pathway component availability can be controlled by endocytosis of receptors, transcription or translation of pathway components, and protein degradation. Recent findings suggest integrin-containing clathrin lattices sequester EGFR, keeping a subpopulation at the membrane rather than being endocytosed and recycled (Alfonzo-Méndez et al., 2022). The availability of receptor copy number can impact different receptors that compete for the same substrates. For example, EGFR and EphA2 receptors display cell type-specific variation in expression levels which contributes to their ability to compete for Grb2 and SOS binding (Oh et al., 2022). Pathway A can also alter the availability of ligand for pathway B. For example, the GPCR angiotensin II receptor activates ADAM proteases to trigger EGF ligand release (Eguchi et al., 2001; Thomas et al., 2002). Therefore, GPCR activity can control ligand availability for EGFR activation.

7 | CONTRIBUTION OF RECEPTOR CROSSTALK DYSREGULATION IN DISEASE

Crosstalk between signaling pathways is common in human cells and helps provide the cell with a comprehensive picture of its surroundings. These described mechanisms create flexibility in a cell's response to its environment allowing for adaptation. However, crosstalk between signaling pathways can also contribute to the progression of diseases such as chronic lung disease, neuroinflammatory disease, and cancer (Qu et al., 2019; Z. Sun et al., 2022). In fact, crosstalk has been identified as a major avenue for both disease progression and therapy resistance in cancer (Hassanein et al., 2021; Lai et al., 2018). Unfortunately, nearly every type of cancer benefits from receptor signaling crosstalk as a mechanism to amplify uncontrolled cellular proliferation, adhesion-independent survival, and metastatic invasion and migration. Many receptors and their downstream targets are considered oncogenes. For example, EGFR-family of receptors and their downstream targets Ras, Raf, Src, and Lck are factors that promote oncogenesis (Miller & Miller, 2012). Integrins and RTKs can further exacerbate tumorigenesis (Javadi et al., 2020). Moreover, integrin-EGFR crosstalk in cancers contributes to signaling dysregulation and disease progression through all the mechanisms described above. Integrin activation promotes EGFR pathway component transcriptional upregulation and EGFR endocytosis and turnover (Carpenter et al., 2015; Morello et al., 2011). Additionally, Src-mediated phosphorylation of EGFR in breast cancer cells enhances DNA synthesis of tumor cells (Biscardi et al., 1999). Interestingly, crosstalk between integrins and EGFR can not only activate EGFR itself, but also direct alternative pathway activation downstream of EGFR. Cross-linking of α6β4-integrin can cluster EGFR to promote Rho activation rather than canonical Akt or Erk activation in triple-negative breast carcinoma cells (Gilcrease et al., 2009). Conversely, in other disease contexts, integrin activation can negatively regulate EGFR activity. Paradoxically, in colorectal cancer cells, integrin α5β1 clustering decreases EGFR and HGFR phosphorylation and Akt signaling, instead activating GSK3 and speculative

endocytosis pathways (Starchenko et al., 2021). This illustrates the complexity of receptor crosstalk directing alternative downstream signaling.

Targeted therapy of signaling pathways upregulated in cancers has been met with some success; however, many challenges remain. In particular, the treatment of lung adenocarcinoma and breast cancers with RTK and MAPK inhibitors often leads to therapy resistance and disease recurrence (Alexander & Wang, 2015; Kun et al., 2021). Several mechanisms of drug resistance are driven by additional acquired mutations that overcome inhibition. However, resistance can also be achieved through pathway crosstalk which bypasses inhibition of one receptor to allow downstream activation. For example, EGFR and β1-integrin crosstalk improves cancer cell survival upon radiation (Vehlow & Cordes, 2022). Moreover, shared downstream effectors of RTKs such as components of the MAPK and PI3K pathways can be activated by a variety of upstream receptors. This, in turn, presents difficulty in disease treatment. For example, KRAS-mutated colorectal cancer cells can resist MAPK/MEK inhibition by activating PI3K through other RTKs, including HER2, HER3, and IGF1R (Vitiello et al., 2019). While navigating drug resistance mechanisms in cancers remains a challenge, efforts to identify activated crosstalk pathways during drug resistance and alternative combinatorial therapeutic approaches are promising (Jaeger et al., 2017). Future studies identifying combinatorial approaches that target crosstalk mechanisms in diseases such as cancer will be important in overcoming barriers to drug resistance.

8 | CONCLUDING REMARKS

Cells within an organism experience a multifaceted environment and are exposed to chemical, spatial, and physical inputs simultaneously. The current understanding of how cells sense their external environment is extensive, yet incomplete. Open questions in the field include the basis for cell type-specific responses, how the environment impacts signaling outputs, and how multiple signaling pathways and receptors are integrated to determine the cellular response.

Recently, research in the signal transduction field has identified phase separation as another potential mechanism to regulate receptor organization and activation (Case, Ditlev, & Rosen, 2019). Phase separation occurs when it is energetically favorable for a solution to demix, and phase separation contributes to the formation of biomolecular condensates throughout the cell (Yongdae & Brangwynne, 2017). At the plasma membrane, phase separation can promote clustering of receptors, including RTKs, integrins, the cell-adhesion receptor nephrin, and the linker for activation of T-cell (LAT) receptor (Banjade & Rosen, 2014; Case et al., 2022; Case, Ditlev, & Rosen, 2019; Mayer & Yu, 2018; Su Xiaolei et al., 2016; Lin et al., 2022a; Lin et al., 2022b). In some cases, phase separation of receptors has been observed to enhance downstream signaling (Case, Zhang, et al., 2019; W. Y. C. Huang et al., 2019). However, additional studies are needed to understand the potential functional consequences of phase separation for signaling and crosstalk in cells.

Crosstalk of signaling pathways is further complicated by the overlapping use of adaptor proteins and downstream effectors by multiple pathways. For example, Grb2 can bind to Gab1, SOS, RTKs, PI3K, and Cbl through its SH2 and SH3 domains (Buday et al., 1996; Egan et al., 1993; McDonald et al., 2012). We do not fully understand how a finite pool of adaptor protein, such as Grb2, is partitioned across all receptors in a cell at any given moment. Spatiotemporal tracking of individual adaptor proteins in live cells and tissues exposed to intricate ligand environments is an approach to studying this problem (Freeman et al., 2012; Wintgens et al., 2019). Finally, how cells sense and integrate information from their environment changes during disease progression, and it is important to understand how crosstalk mechanisms change between healthy and diseased cells and tissue.

AUTHOR CONTRIBUTIONS

Maria F. Ullo: Conceptualization (equal); writing – original draft (lead); writing – review and editing (equal). **Lindsay B. Case:** Conceptualization (equal); funding acquisition (lead); supervision (lead); writing – original draft (supporting); writing – review and editing (equal).

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Ullo, M. F., & Case, L. B. (2023). How cells sense and integrate information from different sources. *WIREs Mechanisms of Disease*, e1604. https://doi.org/10.1002/wsbm.1604