# Common and Distinct Elements in Cellular Signaling via EGF and FGF Receptors

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**Signaling pathways that are activated by epidermal growth factor (EGF) or fibroblast growth factor (FGF) receptors have been identified and compared (detailed Connections Maps are available at *Science*'s Signal Transduction Knowledge Environment). Both receptors stimulate a similar complement of intracellular signaling pathways. However, whereas activated EGF receptors (EGFRs) function as the main platform for recruitment of signaling proteins, signaling through the FGF receptors (FGFRs) is mediated primarily by assembly of a multidocking protein complex. Moreover, FGFR signaling is subject to additional intracellular and extracellular control mechanisms that do not affect EGFR signaling. The differential circuitry of the intracellular networks that are activated by EGFR and FGFR may affect signal specificity and physiological responses.**

The human genome contains 59 genes that encode 20 distinct families of receptor tyrosine kinases (RTKs) (*1*). In response to stimulation by specific ligands, RTKs regulate a great diversity of cellular processes (*2*), including cell survival, proliferation and differentiation, cell metabolism, and cell migration. Dysfunctions in RTKs and their signaling pathways have been linked to diabetes, atherosclerosis, severe developmental pathologies, and various cancers (*3*). The EGF receptor (EGFR) family comprises four members designated EGFR, ErbB2, ErbB3, and ErbB4 (*4*). The intrinsic protein tyrosine kinase (PTK) activities of these receptors and their abilities to recruit and activate intracellular signaling pathways are controlled by members of the EGF family of growth factors. Although certain members of the EGFR family can be activated by several EGF family members (e.g., EGFR), others do not directly bind any ligand (e.g., ErbB2) or are devoid of intrinsic PTK activity (e.g., ErbB3). Therefore, the action of ErbB3 and ErbB2 are dependent upon combinatorial interactions with other members of the EGFR family that are stimulated by EGF, transforming growth factor α (TGF-α), heparin-bound EGF (HB-EGF), or other EGF family members (*4*).

The fibroblast growth factor receptor (FGFR) family also comprises four RTKs designated FGFR1, FGFR2, FGFR3, and FGFR4 (*5*). An important hallmark of FGFRs is that the diversity of this RTK family is controlled by alternative RNA splicing, resulting in the generation of multiple splice variants (*6*) in the extracellular domains that exhibit distinct tissue expression patterns and differential ligand-binding characteristics toward the 22 known FGFs. Consequently, a single *Fgfr* gene can encode two receptors that exhibit different FGF-binding characteristics (*6*) and that are expressed in different tissues (i.e., mesenchyme, epithelium).

In this Viewpoint, we compare key features underlying the action of EGFRs and FGFRs that may lead to their unique pleiotropic responses and physiological roles. This comparison may provide insights into one of the key open questions in cell signaling, that is, how signaling specificity is generated following stimulation of a common complement of signaling pathways by a given RTK.

Before ligand stimulation, intramolecular interactions within the extracellular domains of each of the EGF and FGF receptors maintain the two receptors in an inactive monomeric state (*7*). Both receptors are activated by ligand-induced dimerization, tyrosine autophosphorylation, and stimulation of their intrinsic PTK activities (*2*). Moreover, similar repertoires of intracellular signaling pathways are stimulated by both RTKs (*2*). Yet, inspection of the various steps involved in the action of the two receptors shows that signaling through FGFR involves additional layers of control that take place both inside and outside the cell.

EGFR is activated by the binding of one type of ligand molecule (i.e., EGF, TGF-α) (*2*, *4*); in contrast, the activation of FGFR involves two different ligands, FGF and heparan sulfate proteoglycan (HSPG), that act together to activate FGFRs (*2*, *8*). The binding of each ligand alone is insufficient for stabilization of FGFR dimerization, a prerequisite for tyrosine autophosphorylation and stimulation of the intrinsic PTK activity. HSPG increases the binding affinity of FGF to FGFR and stabilizes FGFR dimerization and activation. Furthermore, it is thought that FGF bound to HSPG in the extracellular matrix may provide a store of FGF molecules.

Comparison of EGFR and FGFR signaling pathways that are summarized in the STKE Connection Maps (*9*, *10*) shows that, for the most part, a similar repertoire of signaling proteins are recruited and activated by the two receptors. Yet, the regulation of the signaling pathways by FGFR is less direct, involving additional layers of control. In the case of EGFR, tyrosine autophosphorylation sites on the receptor function as the main platform for recruitment of signaling components that are activated by EGF signaling (*2*, *11*). In addition, some signaling pathways are activated by accessory proteins that are tyrosine phosphorylated by EGFR (Fig. 1). In contrast, a docking protein (FRS2) that is tyrosine phosphorylated by FGFR (*12*) recruits the lion's share of the signaling components that are activated by FGF stimulation, and only a few signaling pathways are activated by direct interactions with the FGFR (Fig. 1).

Tyrosine autophosphorylation sites located in the C terminus of EGFR (*13*) function as binding sites for the adaptor proteins Grb2, Nck, and Shc; for phospholipase Cγ (PLC-γ); and for the transcription factor, STAT1 (*9*). Grb2 molecules are recruited by EGFR directly and indirectly through tyrosine-phosphorylated Shc, leading to the activation of the Ras–mitogen-activated protein kinase (MAPK) cascade (*9*, *14*). Recruitment to the membrane and tyrosine phosphorylation enhance the enzymatic activity of PLC-γ, leading to the formation of two second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate ($IP_3$). $IP_3$ releases $Ca^{2+}$ from internal stores, which in turn acts in concert with DAG to translocate protein kinase C (PKC) to the cell membrane and stimulate its enzymatic activity (*9*). PKC then phosphorylates and regulates the activity of many proteins, including EGFR; phosphorylation of a threonine residue ($Thr^{654}$) in the juxtamembrane domain modulates EGF binding affinity and kinase activity of the EGFR (*15*). Nck may link the EGFR with the actin cytoskeleton (*9*), and tyrosine phosphorylation of STAT1 leads to transcription of genes that regulate cell cycle arrest (*9*). In addition, EGF stimulates a cell survival pathway mediated by phosphoinositide 3-kinase (PI3K) and the protein kinase Akt (*16*) by an indirect mechanism in which tyrosine phosphorylation of the docking protein Gab1 or ErbB3 by EGFR leads to recruitment and activation of PI3K.

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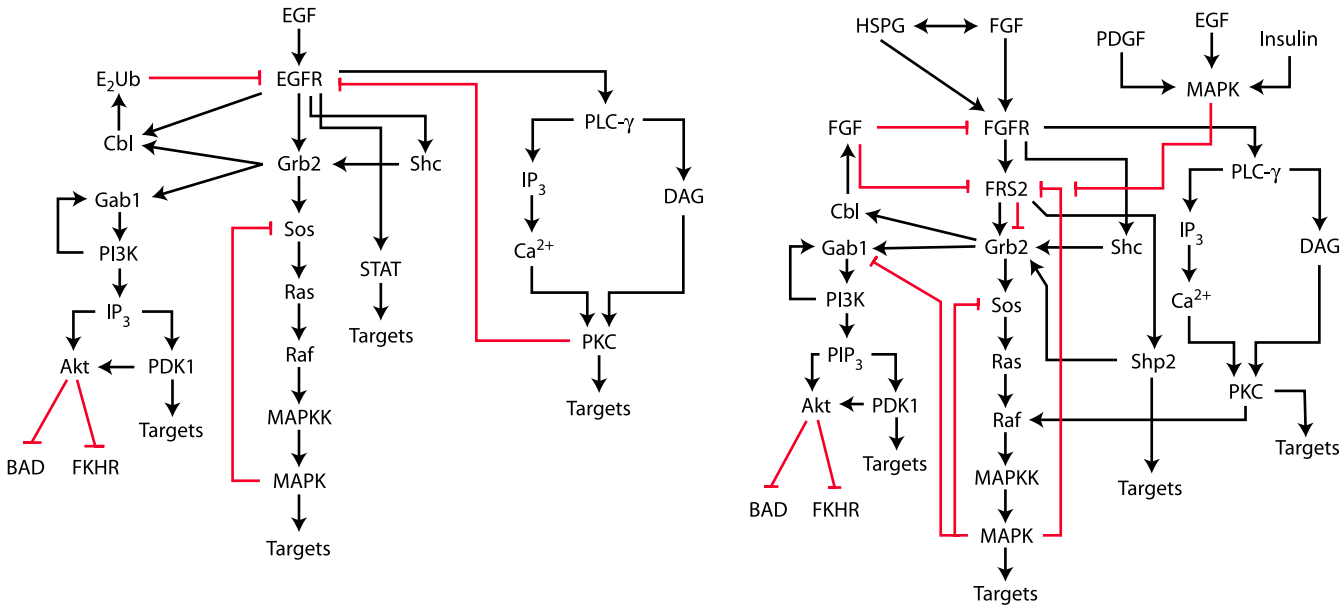


**Fig. 1.** Cell signaling by EGF or FGF receptors. An abbreviated version of signaling by EGFR (left) and FGFR (right). Detailed description is presented in STKE Connections Maps (*9*, *10*). Stimulatory and inhibitory stimuli are depicted in black and red, respectively. Abbreviations: HSPG, heparan sulfate proteoglycan; $E_2$Ub, ubiquitin-conjugating enzyme; $IP_3$, inositol 1,4,5-triphosphate; $PIP_3$, phosphatidylinositol 3,4,5-trisphosphate. Additional abbreviations are in the text and in the Connections Maps (*9*, *10*).

Although the signaling pathways activated by FGFRs substantially overlap with those activated by EGFRs, the pathways are activated through the formation of a multidocking protein complex induced by tyrosine phosphorylation. Tyrosine phosphorylation of FRS2 leads to recruitment of four Grb2 molecules directly and two Grb2 molecules indirectly through tyrosine phosphorylation of the protein tyrosine phosphatase Shp2 in complex with FRS2. Grb2 molecules bound to FRS2 recruit the nucleotide exchange factor SOS, leading to the activation of the Ras-MAPK signaling cascade. In addition, Grb2 recruits the docking protein Gab1, which is tyrosine phosphorylated by FGFR, leading to recruitment and activation of the PI3K-Akt cell survival pathway (*16*, *17*).

Differences in the mechanisms of negative regulation between FGFR and EGFR are also apparent, despite involving similar regulatory elements. The ubiquitin ligase Cbl interacts with EGFR directly and indirectly through Grb2, promoting ubiquitination and degradation of EGFR (*18*). Grb2, bound to Cbl, does not interact directly with FGFR but, rather, binds to tyrosine-phosphorylated FRS2, promoting ubiquitination and degradation of FRS2 and FGFR (*19*). FRS2 is also the site of an additional negative-feedback loop from MAPK, which is absent in the EGFR pathway. The binding of tyrosine-phosphorylated Sprouty to the SH2 domain of Grb2 sequesters Grb2 and prevents its binding to the activated EGFR or FRS2, causing attenuation of the Ras-MAPK cascade in EGF and FGF signaling (*18*, *20*). However, it was proposed that Sprouty may play a bimodal negative and positive role in regulation of signaling through EGF and other RTKs (*20*).

Although both EGFR and FGFR stimulate a similar repertoire of canonical intracellular signaling pathways, signaling by FGFR is more complex and subject to additional control mechanisms. The less stringent control of EGFR activity may explain why overexpression of EGFR and ErbB2 occurs frequently in different cancers (*3*). If signaling pathways are viewed as components of intracellular networks, the specificity generated by an intracellular network may be affected by layers of control that may influence signal duration, signal amplitude, and spatial localization of key regulatory elements. In addition, inhibitory signals promoted by cross talk between RTKs (*21*); by protein phosphatases, receptor endocytosis, and degradation; and by other negative-feedback mechanisms may also affect signal specificity and biological outcome (*22*).

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