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Minireview

Molecules and Cells

Asymmetric Tyrosine Kinase Arrangements in Activation or Autophosphorylation of Receptor Tyrosine Kinases

Jae Hyun Bae*, and Joseph Schlessinger

Receptor tyrosine kinases (RTKs) play important roles in the control of many cellular processes including cell proliferation, cell adhesion, angiogenesis, and apoptosis. Ligand-induced dimerization of RTKs leads to autophosphorylation and activation of RTKs. Structural studies have shown that while isolated ectodomains of several RTKs form symmetric dimers the isolated cytoplasmic kinase domains of epidermal growth factor receptor (EGFR) and fibroblast growth factor receptor (FGFR) form asymmetric dimers during their activation. Binding of one kinase molecule of EGFR to a second kinase molecule asymmetrically leads to stimulation of kinase activity and enhanced autophosphorylation. Furthermore, the structures of the kinase domain of FGFR1 and FGFR2 reveal the formation of asymmetric interfaces in the processes of autophosphorylation at their specific phosphotyrosine (pY) sites. Disruption of asymmetric dimer interface of EGFR leads to reduction in enzymatic activity and drastic reduction of autophosphorylation of FGFRs in ligand-stimulated live cells. These studies demonstrate that asymmetric dimer formation is as a common phenomenon critical for activation and autophosphorylation of RTKs.

INTRODUCTION

Receptor tyrosine kinases (RTKs) play a critical role in the control of many fundamental cellular processes including cell proliferation and differentiation, cell metabolism, cell migration and cell survival (Hunter, 2000; Pawson et al., 2001; Schlessinger, 2000). Due to their critical role in the control of these cellular processes many diseases are caused by aberrant RTK activation or overexpression. All RTKs are composed of an extracellular ligand binding region, a single transmembrane helix and a cytoplasmic region containing a tyrosine kinase domain. The 58 RTKs found in the human genome are classified into 20 families based on their amino acid sequence similarities, their structural architectures and biological functions. Prior to ligand stimulation most RTKs are displayed on the surface of cells in the form of monomers that are in equilibrium with a small population of receptor dimers, and ligand binding to the extracellular domain stimulates RTK dimerization (Fig. 1). Numerous studies have shown that ligand-induced RTK dimerization is responsible for autophosphorylation, stimulation of tyrosine kinase activity and cell signaling (Pawson, 1994; Schlessinger, 2000; van der Geer et al., 1994). While autophosphorylation of tyrosines in the catalytic core is critical for stimulation of the tyrosine kinase activity, tyrosine phosphorylation sites in other parts of the cytoplasmic region of RTKs serve as specific binding sites for downstream signaling molecules containing Src Homology 2 (SH2) domain (Sadowski et al., 1986) or phosphotyrosine binding (PTB) domains (van der Geer and Pawson, 1995). Signaling molecules docked on RTKs through their SH2 or PTB domains are phosphorylated resulting in activation of specific signaling pathways.

Determination of the crystal structures of ligand-induced dimers of the extracellular regions of EGFR (Cho and Leahy, 2002; Garrett et al., 2002; Ogiso et al., 2002), FGFR1 (Mohammadi et al., 1996; Plotnikov et al., 1999; 2000; Schlessinger, 2000) and KIT (Yuzawa et al., 2007) revealed 2 fold symmetric arrangements of ligand-induced dimers of the extracellular regions of these receptors. However, structural analysis of the tyrosine kinase domain of EGFR revealed formation of an asymmetric kinase dimer with an arrangement shown to be essential for tyrosine kinase activation (Zhang et al., 2006). Asymmetric homodimer formation of the tyrosine kinase domains of FGFR1 or FGFR2 was also revealed by structural analyses of these regions (Bae et al., 2010; Chen et al., 2008). Moreover, the asymmetric dimer arrangements of the tyrosine kinase domain of FGFR1 were shown to be essential for trans autophosphorylation of FGFR1 in living cells (Bae et al., 2010).

Epidermal Growth Factor Receptor (EGFR)

EGFR was discovered as the first RTK (Carpenter and Cohen, 1977) and subsequently shown to be a member of a family composed of four RTKs including EGFR, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4. The structural basis for ligand-induced dimerization of the EGFR extracellular domains is now well established (Cho and Leahy, 2002; Cho et al., 2003; Garrett et al., 2002; 2003; Ogiso et al., 2002). Like most RTKs prior to ligand stimulation the EGFR exists on cell surface of living cells predominantly as monomers that are in the equilib-

Department of Pharmacology, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06520-8066, USA
*Correspondence: jaehyun.bae@yale.edu

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rium with a small population of EGFR dimers (Burgess et al., 2003; Ferguson et al., 2003). In response to ligand binding a conformational change occurs in EGFR monomers that are maintained in a tethered autoinhibited conformations leading to formation ligand bound dimeric EGFR extracellular domain complexes (Cho and Leahy, 2002; Cho et al., 2003; Garrett et al., 2002; 2003; Ogiso et al., 2002). EGFR dimerization brings the transmembrane and cytoplasmic regions of two neighboring molecules into close proximity resulting in direct contacts between the tyrosine kinase domains of two receptor protomers (Yarden and Schlessinger, 1987; Zhang et al., 2006). Stimulation of the kinase activity of EGFR leads to trans autophosphorylation on multiple tyrosine residues that are located primarily in the c-terminal tail of EGFR (Hazan et al., 1990; Margolis et al., 1989). It was shown that the phosphotyrosines located at the c-terminal tail of EGFR serve as docking sites for downstream signaling proteins (Avivi et al., 1991; Margolis et al., 1990; Rotin et al., 1992). Structural studies revealed both symmetric and asymmetric arrangements of EGFR kinase domains in crystal lattice (Jura et al., 2009; Red Brewer et al., 2009; Wood et al., 2004; Zhang et al., 2006). The asymmetric EGFR dimer structure resembles that of cyclin-dependent kinase 2 (CDK2) in complex with its activator, cyclin A (Fig. 2A) (Jeffrey et al., 1995; Russo et al., 1996). In the CDK2/cyclin A complex, cyclin A acts as an activator (donor) for the CDK2 conformational change and CDK2 as a receiver (acceptor) to be activated. One of two helical domains of cyclin A interacts with one side of activation loop on the N-lobe, C-lobe of CDK2, and the helix α1 (generally called as the helix αC) containing characteristic PSTAIRE motif (Fig. 2B). This complex formation realigns interactions among residues of CDK2 to stabilize an open conformation of the activation loop resulting in the basal CDK2 kinase activity. Full activation of CDK2 is mediated by the phosphorylation of a specific threonine (T160) on the activation loop of CDK2 and by an additional conformational change.

In the asymmetric EGFR dimer structure, one kinase domain takes the role of cyclin A in CDK2/cyclin A complex while the second EGFR kinase domain takes the role of CDK2 (Zhang et al., 2006). One EGFR kinase domain functions as an activator (donor) and the other kinase domain serves as a receiver (acceptor) that is activated by interactions similar to those seen in the CDK2/cyclinA complex structure (Jeffrey et al., 1995; Russo et al., 1996). The activator EGFR makes contacts to the receiver EGFR primarily through interactions between helices αH and αI of the C-lobe of the activator EGFR with the juxtamembrane region and helix αC of the N-lobe of the receiver EGFR molecule. Zhang et al showed that EGFR activation is inhibited by mutation that disrupts the formation of the asymmetric interface (Zhang et al., 2006). Moreover, introduction of reverse-charge mutations on helices (αH or αI) of EGFR C-lobe (R938E, I942E, and K946E) or on N-terminal region of EGFR N-lobe (P675G, L680N, and I682Q) resulted in the loss of kinase activity of ligand stimulated EGFR. In addition, the inhibitory MIG6-derived peptide, which blocks EGFR activation (Hackel et al., 2001), binds to the same asymmetric interface of EGFR dimer. These experiments show that the asymmetric formation of EGFR dimers is required for EGFR activation (Zhang et al., 2007). It was recently demonstrated that the juxtamembrane region of EGFR is involved in the activation of EGFR by forming asymmetric homodimer (Jura et al., 2009; Red Brewer et al., 2009). The juxtamembrane region of EGFR connects the single-helical transmembrane region to tyrosine kinase domain, and is divided into two parts. The first half of the juxtamembrane region (JM-A; aa645-663) is helical and forms an anti-parallel dimer with the juxtamembrane region of a second EGFR molecule. The second half of the juxtamembrane region (JM-B; aa664-682) facilitates formation of asymmetric dimer of the kinase domains of EGFR. The second half of the juxtamembrane (JM-B) of the receiver (acceptor) EGFR makes contacts with the C-lobe of activator (donor) EGFR through hydrophobic interactions, and stabilizes asymmetric complex formation. In contrast, the second half of the activator EGFR is stretched and interacts to its kinase domain surface. Biochemical experiments showed that kinase activity of EGFR is compromised by deletion of the juxtamembrane region. In addition, single reverse-charge mutants on the second half of juxtamembrane (JM-B) interacting to helices of C-lobe of the activator EGFR (R622G, L664R, V656R, and L668R) or on C-lobe of receiver EGFR (D950A, R953A, R949E, and N972A) lost their kinase activities. These results demonstrate that the juxtamembrane region facilitates asymmetric dimer formation and EGFR activation.

In the symmetric inactive dimer of EGFR, a helical region (AP-2) is identified in the middle of the C-terminal tail (Landau et al., 2004). In the head-to-head dimer of inactive EGFR structure, both molecules show that the helix of the C-terminal tail of one EGFR is embedded between its hinge region and the N-lobe of the other EGFR by formation of the electrostatic hook stacking hydrophobic residues in between (Jura et al., 2009; Landau et al., 2004). The disruption by mutation on the electrostatic hook of EGFR symmetric dimer (D979K/E980R and E981R/D982K) activates autophosphorylation of EGFR. This finding suggests that a helix in the EGFR C-terminal tail mediates formation of a symmetric auto-inhibitory dimer. Accordingly, binding of EGF to the extracellular region of EGFR causes a conformational change that is followed by formation of an asymmetric kinase dimer formation and EGFR activation.

Fibroblast Growth Factor Receptors (FGFRs)

FGFRs play important roles in the control of many biological processes including early embryonic development (Dailey et al., 2005; Katoh, 2006; Robinson, 2006), cell adhesion (Hall et al., 1996), proliferation (Boilly et al., 2000), and bone formation (Naski and Ornitz, 1998). It is now well established that several developmental disorders are caused by gain or loss of function FGFR mutation. (Beenken and Mohammadi, 2009; Wilkie, 2005). A variety of human cancers are also driven by gain of function FGFR mutations. (Ezzat and Asa, 2005; Knights and Cook, 2010). Like other RTKs the four members of the FGFR family are activated by the ligand induced receptor dimerization followed by tyrosine kinase activation and autophosphorylation of specific tyrosine residues in the cytoplasmic region; a process shown to be mediated by a precise and sequential ordered reaction (Furdui et al., 2006; Lew et al., 2009).

Atomic structures of activated kinase domains of FGFR1 (Bae et al., 2009; 2010) and FGFR2 (Chen et al., 2008) have elucidated intermediate states of autophosphorylation events of FGFRs (Figs. 2C and 2D). These structures showed asymmetric formation of FGFR1 or FGFR2 kinase domains wherein one molecule serves as an enzyme that phosphorylates a specific tyrosine residue on the second kinase molecule (the substrate). This enzyme-substrate relationship in FGFRs is different from the activator-receiver relationship observed in structures of EGFR asymmetric homodimer.

The atomic structure of activated FGFR1 kinase domain in complex with the deletion construct of PLCγ has shown that the activated FGFR1 kinase domains in the crystal lattice form an asymmetric dimer (Fig. 2C) (Bae et al., 2009). In this structure, the kinase insert of one kinase domain is bound to the sub-

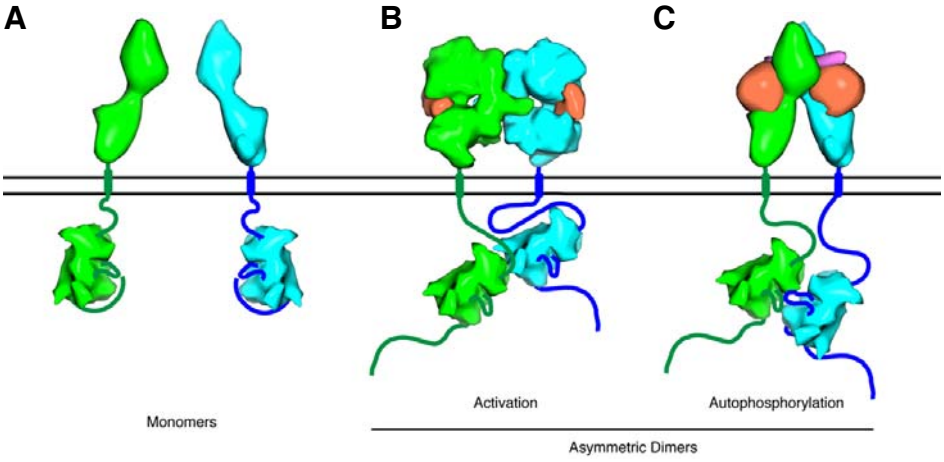

Fig. 1. Various statuses of receptor tyrosine kinases (RTKs) on cell surface. (A) Monomeric forms of a RTK on cell surface are illustrated. Extracellular domain, a single strand transmembrane domain, the juxtamembrane region, kinase domain and the C-terminal region of a RTK are shown from top to bottom. The activation loop in the kinase domain is indicated. Two black solid lines in the middle represent the cell membrane. (B) Asymmetric dimer formation in the activation of EGFR. Ligand-induced conformational change in the extracellular domains of EGFR triggers the asymmetric dimer formation of EGFR kinase domains. One EGFR kinase domain in cyan (activator; donor) activates the other EGFR kinase domain in green (receiver; acceptor). The juxtamembrane regions of both EGFR interacts each other to stabilize the asymmetric dimer with their first halves, and the second half of the receiver EGFR makes contacts with C-lobe of activator EGFR. (C) In the event of trans autophosphorylation, cytoplasmic domains of a RTK form asymmetric dimer (derived from activated FGFR1 and FGFR2 dimer structures). One kinase domain of a RTK colored in green (enzyme-acting kinase) phosphorylates a specific tyrosine site of the other kinase domain colored in cyan (substrate-acting kinase) *in trans* by the asymmetric dimer formation.

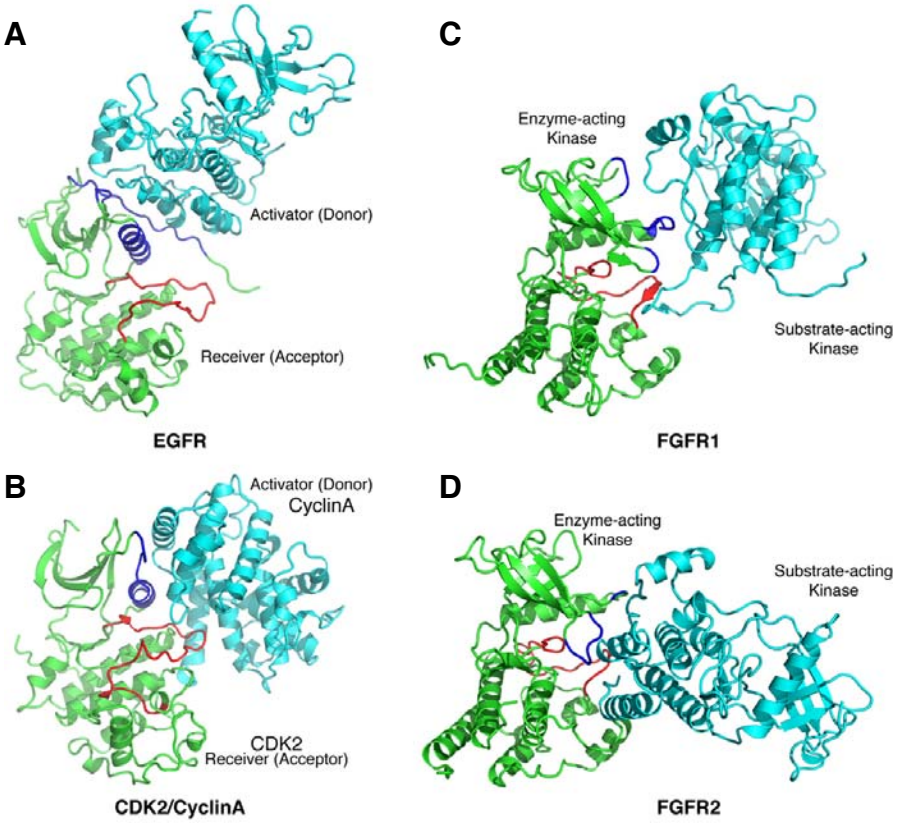

Fig. 2. Asymmetric dimers of various RTKs and CDK2/cyclin A complex. (A) Dimer formation in the event of initial activation of EGFR (PDB code: 2GS6). The activator (donor) is colored in cyan, and the receiver in green. Activation loop of the receiver colored in red shows the open conformation, and the asymmetric contact region of the receiver is colored in blue. The color code indicated here is followed throughout Fig. 2. Mainly the helix αC and juxtamembrane region of the receiver EGFR are involved in the formation of the asymmetric contact region. (B) Complex structure of CDK2 and Cyclin A (PDB code: 1FIN). The helix α1 (in general, called as αC) and adjacent residues of CDK2 makes asymmetric contacts with one of helical domains of Cyclin A. (C) Dimer formation of activated FGFR1 kinase domains in trans autophosphorylation event (PDB code: 3GQI). Phosphotyrosine site (Y583) in the kinase insert of one FGFR1 (substrate-acting kinase) is bound to the catalytic cleft of the other (enzyme-acting kinase) resulting in the asymmetric dimer formation. (D) Dimer formation of activated FGFR2 in the event of trans autophosphorylation (PDB code: 3CLY). The phosphotyrosine site (Y769) of an activated FGFR2 (substrate-acting kinase) is bound to the catalytic cleft of the other FGFR2 kinase domain (enzyme-acting kinase) like activated FGFR1 dimer. In both FGFR1 and FGFR2 homodimers, nucleotide-binding loops are involved in asymmetric yet distinctive homodimer formation.

strate-binding site of a second symmetry-related activated FGFR1 kinase domain forming a unique asymmetric interface. The asymmetric interface is formed between the activation segment together with the N-lobe of the enzyme-acting FGFR1 kinase domain and the kinase insert as well as the C-lobe of the substrate-acting FGFR1. The asymmetric kinase interface can be divided into two regions according to the vicinity to the substrate-binding site on the catalytic cleft, designated the

proximal and the distal substrate-binding regions. The proximal substrate-binding region includes the direct interface between the substrate (Y583F) of the substrate-acting kinase and the catalytic cleft of the enzyme-acting kinase, and the distal substrate-binding region includes the extended interface from the proximal region between N-lobe of the enzyme-acting FGFR1 and C-lobe of substrate-acting FGFR1. The nucleotide-binding loop (part of the N-lobe) of the enzyme-acting FGFR1 and the helix G (αG) of the C-lobe of the substrate-acting FGFR1 are involved in the formation of the distal substrate-binding region.

In the distal substrate-binding region, R577 on the kinase insert of the substrate-acting FGFR1 makes strong contact to D519 of the enzyme-acting FGFR1. The physiological function of the distal substrate-binding region has been examined by the introduction of the reverse-charge mutation on R577 to glutamic acid. The reverse-charge mutation resulted in the reduction of the kinase activity of the isolated mutant FGFR1 kinase domain (Bae et al., 2010). This reverse-charge mutation on the intact FGFR1 expressed in living L6 myoblast caused a dramatic reduction in autophosphorylation of intact ligand-stimulated FGFR1 while the same FGFR1 mutant exhibited normal *in vitro* tyrosine kinase activity. Furthermore, the atomic structure of the FGFR1 R577E mutant is virtually identical to the structure of wild type FGFR1 kinase domain structure except for differences in the kinase insert region caused by the high flexibility of this region as well as crystal packing (Bae et al., 2010). The unchanged overall conformation of R577E mutant of FGFR1 implies that the compromised autophosphyration observed in live cells is not caused by impairment of kinase activity but rather due to the disruption of the asymmetric kinase interface.

In the FGFR2 asymmetric dimer, the activation segment of FGFR2 kinase domain is maintained in open conformation to facilitate phosphorylation by enabling the substatre access to the catalytic cleft (Fig. 2D) (Chen et al., 2008). In this structure, Y769 of one FGFR2 molecule (substrate-acting) is bound to the substrate-binding site of the second symmetry-related FGFR2 kinase domain (enzyme-acting). The enzyme-acting FGFR2 harbors the substrate-acting FGFR2 C-terminal tail containing Y769; an amino acid that functions as the docking site of PLCγ (Mohammadi et al., 1991). The binding mode of the substrate (Y769) in the intermediate state dimer is virtually identical to that of a peptide bound to the activated FGFR2 structure (PDB code: 2PVF) (Chen et al., 2007). In the asymmetric FGFR2 dimer, the C-lobe (including the C-terminal tail) of substrate-acting FGFR2 interacts with the catalytic cleft region of the C-lobe as well as the N-lobe (including the nucleotide-binding loop) of the enzyme-acting FGFR2. The asymmetric interface formed in FGFR2 dimer like in the FGFR1 asymmetric dimer can be divided into two regions, the proximal and the distal substrate-binding regions. The proximal substrate-binding region of FGFR2 includes the catalytic cleft of enzyme-acting FGFR2 and the vicinity of the substrate (Y769) of the substrate-acting FGFR2. The distal substrate-binding region of FGFR2 dimer is formed mainly between the nucleotide-binding loop of the enzyme-acting FGFR2 N-lobe and the helix G (αG) of the substrate-acting FGFR2 C-lobe. The disruption of the interface in FGFR2 asymmetric dimer by mutations (F600A, N730A, N766A, E767A, L770A, D771A, and L772A) led to reduced *in vitro* kinase activity and reduced phosphorylation of Y769 of a kinase-negative FGFR2 mutant (Chen et al., 2008).

Interestingly, nucleotide-binding loops from the enzyme-acting kinase domains of either FGFR1 (Bae et al., 2010) and FGFR2 (Chen et al., 2008) homodimers are involved in the formation of the distal substrate-binding regions. This implies that the nucleotide-binding loop forms not only the ATP binding pocket with one surface but also the distal substrate-binding site for specific phosphotyrosine sites with the other surface. In addition, the distal substrate-binding region of FGFR1 dimer has the different surface profile from that of FGFR2 dimer. These findings suggest that the surface opposite to the ATP binding pocket of the nucleotide binding loop (the distal substrate-binding site) may function as the regulatory interface together with the proximal substrate-binding region to select the specific autophosphorylation sites of RTKs. Furthermore, the difference in distal substrate-binding regions may play a role in the control of sequential autophosphorylation of RTKs. Accordingly, formation of different asymmetric kinase interfaces in activated FGFR1 and FGFR2 kinase may provide the mechanism underlying ordered receptor autophosphorylation. In other words, once a tyrosine from the substrate-acting kinase domain is engaged to the catalytic cleft of the enzyme-acting kinase domain and if both surfaces of substrate-acting and enzyme-acting kinase domains for the proximal substrate-binding region are complementary, the interface is formed between kinase domain dimers. The interface of the proximal substrate-binding region will enable the formation of an additional predetermined interface of the distal substrate-binding region to enhance the binding affinity of the phosphorylation reaction. With the formation of the interface of the distal substrate-binding region, the specific tyrosine bound to the catalytic cleft will be phosphorylated *in trans* by the enzyme-acting kinase domain.

FUTURE PERSPECTIVES

Despite of the relatively abundant structural information on RTK kinase domains, it is still not clear how RTKs initiate and process their autophosphorylation reaction during the activation. Like the asymmetric homodimers of EGFR, FGFR1 and FGFR2, structural studies on the dimer formations of other RTKs will help to understand the mechanisms of RTK activation. At the initiation of RTK activation, several prerequisites have to be met like how ligand-induced dimerization influences the cytoplasmic regions including juxtamembrane, kinase and C-terminal regions, and how two kinase domains form the interface to be phosphorylated and eventually activated. In addition, the elucidation of interfaces for each autophosphorylation site of RTKs will lead to better understandings on the controlling mechanisms specifying the phosphorylation sites as well as identifying intermediate interfaces that regulate the autophosphorylation. Furthermore, it is still not known how RTK dimer phosphorylates each other *in trans*, that is, if one fully phosphorylates the other and then takes turns to be phosphorylated by the other molecule, or takes turns one after the other until each molecule reaches to the fully activated forms. It is also not confirmed if the precise sequential order of *in vitro* autophosphorylation shown in FGFR1 kinase domain also occurs *in vivo,* due to technical difficulties in exploring autophosphorylation in live cells. Important new insights concerning the action and regulation of RTKs will emerge when answers to these unsolved questions will be obtained by structural and biochemical studies.

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