Activated point mutants of FGFR2

Ezzat, S., Rothfels, K.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

19/12/2022
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 83

This document contains 1 pathway and 10 reactions (see Table of Contents)
Activated point mutants of FGFR2

Stable identifier: R-HSA-2033519

Compartments: plasma membrane, cytosol, extracellular region

Diseases: cancer, bone development disease

Autosomal dominant mutations in FGFR2 are associated with the development of a range of skeletal disorders including Beare-Stevensen cutis gyrata syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome, Crouzon syndrome and Apert Syndrome (reviewed in Burke, 1998; Webster and Donoghue, 1997; Cunningham, 2007). Mutations that give rise to Crouzon, Jackson-Weiss and Pfeiffer syndromes tend to cluster in the third Ig-like domain of the receptor, either in exon IIIa (shared by the IIIb and the IIIc isoforms) or in the FGFR2c-specific exon IIIc. These mutations frequently involve creation or removal of a cysteine residue, leading to the formation of an unpaired cysteine residue that is thought to promote intramolecular dimerization and thus constitutive, ligand-independent activation (reviewed in Burke, 1998; Webster and Donoghue, 1997; Cunningham, 2007). Mutations in FGFR2 that give rise to Apert Syndrome cluster to the highly conserved Pro-Ser dipeptide in the IgII-Ig III linker; mutations in the paralogous residues of FGFR1 and 3 give rise to Pfeiffer and Muenke syndromes, respectively (Muenke, 1994; Wilkie, 1995; Bellus, 1996). Development of Beare-Stevensen cutis gyrata is associated with mutations in the transmembrane-proximal region of the receptor (Przylepa, 1996), and similar mutations in FGFR3 are linked to the development of thanatophoric dysplasia I (Tavormina, 1995a). These mutations all affect FGFR2 signaling without altering the intrinsic kinase activity of the receptor.

Activating point mutations have also been identified in FGFR2 in ~15% of endometrial cancers, as well as to a lesser extent in ovarian and gastric cancers (Dutt, 2008; Pollock, 2007; Byron, 2010; Jang, 2001). These mutations are found largely in the extracellular region and in the kinase domain of the receptor, and parallel activating mutations seen in autosomal dominant disorders described above.

Activating mutations in FGFR2 are thought to contribute to receptor activation through diverse mechanisms, including constitutive ligand-independent dimerization (Robertson, 1998), expanded range and affinity for ligand (Ibrahimi, 2004b; Yu, 2000) and enhanced kinase activity (Byron, 2008; Chen, 2007).

Literature references


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Dimerization of FGFR2 ligand-independent mutants

**Location:** Activated point mutants of FGFR2

**Stable identifier:** R-HSA-2029983

**Type:** transition

**Compartments:** plasma membrane

**Diseases:** cancer

Point mutations in FGFR2 that are thought to promote ligand-independent dimerization in the context of autosomal bone development disorders have also been identified in endometrial, ovarian, gastric and lung cancer (Greenman, 2007; Dutt, 2008; Davies, 2005; Byron, 2008; Byron, 2010, Pollock, 2007). Although functional studies on these mutations in FGFR2 in cancer cell lines is limited - only the S267P mutation identified in gastric cancer has been demonstrated biochemically to undergo ligand-independent dimerization (Anderson, 1998) - characterization of paralogous mutations in FGFR3 as well as in other mutations that create unpaired cysteine residues in FGFR2 support the notion that these mutant receptors undergo aberrant intermolecular disulphide bond formation that results in constitutive activation (Galvin, 1996; Neilson and Friesel, 1995; Robertson, 1998; d’Avis, 1998)

**Followed by:** Autocatalytic phosphorylation of FGFR2 ligand-independent mutants

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Autocatalytic phosphorylation of FGFR2 ligand-independent mutants

**Location:** Activated point mutants of FGFR2

**Stable identifier:** R-HSA-2029984

**Type:** transition

**Compartments:** plasma membrane, cytosol

**Diseases:** cancer

FGFR2 S267P undergoes ligand-independent dimerization, and appears unable to stably bind FGF2 ligand under the conditions examined (Anderson, 1998). FGFR2b S373C and Y376C are paralogous to the FGFR3 S371C and Y373C mutations that are seen in thanatophoric dysplasia I (Rousseau, 1996; Tavormina, 1995a) and which have been shown to undergo spontaneous dimerization in the absence of ligand (d’Avis, 1998; Adar, 2002). Moreover, other FGFR2 mutations that introduce unpaired cysteine residues have been shown to support formation of intermolecular disulphide bonds (Galvin, 1996; Neilson and Friesel, 1995), supporting the notion that the FGFR2b S373C and Y376C mutants may promote spontaneous receptor dimerization and activation.

**Preceded by:** Dimerization of FGFR2 ligand-independent mutants

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FGFR2b mutants bind an expanded range of ligands

**Location:** Activated point mutants of FGFR2

**Stable identifier:** R-HSA-2033474

**Type:** binding

**Compartments:** plasma membrane, extracellular region

**Diseases:** cancer, bone development disease

Apert syndrome is the most severe of the craniosynostosis syndromes and results almost entirely from two missense mutations in the conserved Ser252 and Pro253 residues in the IgII-IgIII linker of FGFR2 (Wilkie, 1995). These mutations affect both the 'b' and 'c' isoforms, although mutation in the FGFR2c isoform is believed to be more clinically relevant to the development of Apert syndrome (Lomri, 1998). More recently, the same mutations arising somatically have been identified in endometrial and ovarian cancer (Dutt, 2008; Byron, 2008; Pollock, 2007).

The IgII and IgIII domains and the intervening linker of the FGF receptor constitute a binding site for FGFs (Chellaiah, 1999; Stauber, 2000; Plotnikov, 1999). The epithelial isoform FGFR2b binds only to mesenchymally expressed ligands including FGF7 and FGF10 and does not respond to epithelial ligands FGF2, 4, 6, 8 and 9 (Ornitz, 1996). Introduction of the P252W and P252R mutations into FGFR2b allows the aberrant binding and activation by the epithelially expressed ligands FGF 2, 6 and 9, establishing an autocrine signaling loop in epithelial cells. These mutations also increase the binding affinity for the receptor's normal mesenchymal ligands 2- to 8-fold (Yu, 2000; Ibrahimi, 2004b). Based on biochemical and crystal studies, the mutations in the IgII-IgIII linker region are predicted to alter the hydrogen bonding network in this region and may change the conformation and thus the ligand-binding properties of the mutant receptors (Stauber, 2000).

Followed by: Autocatalytic phosphorylation of FGFR2b mutants with enhanced ligand binding

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Autocatalytic phosphorylation of FGFR2b mutants with enhanced ligand binding

Location: Activated point mutants of FGFR2

Stable identifier: R-HSA-2033488

Type: transition

Compartments: plasma membrane, cytosol

Diseases: female reproductive endometrioid cancer, ovarian cancer, cancer

After aberrantly dimerizing in response to epithelially expressed ligands, FGFR2b S252W and P253R mutants are assumed to undergo transautophosphorylation analogous to both the wild-type receptor, although this has not been explicitly demonstrated. Transformation of NIH 3T3 cells with the FGFR2b S252W mutant confers anchorage independent growth and results in increased phosphorylation of FRS2 in a manner that depends on a functional kinase domain (Dutt, 2008). Knock-down or chemical inhibition of other FGFR2-activating mutations identified in endometrial cancer cells has been shown to cause cell death (Byron, 2008).

Preceded by: FGFR2b mutants bind an expanded range of ligands

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FP-1039 acts as a ligand-trap for FGFR2b-binding ligands in endometrial cancer

Location: Activated point mutants of FGFR2

Stable identifier: R-HSA-2077421

Type: binding

Compartments: extracellular region

Diseases: female reproductive endometrioid cancer, cancer

FP-1039 is a soluble fusion protein consisting of the extracellular region of FGFR1c bound to the Fc region of human IgG1. It is capable of binding to a wide range of FGF ligands and thereby prevents activation of multiple FGF receptors. FP-1039 is in Phase I clinical trials in solid malignancies and in Phase II trials for patients with endometrial cancers harbouring the activating mutations S252W and P253R (reviewed in Wesche, 2011).

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FGFR2c mutants bind an expanded range of ligands

**Location:** Activated point mutants of FGFR2

**Stable identifier:** R-HSA-2033472

**Type:** binding

**Compartments:** plasma membrane, extracellular region

**Diseases:** female reproductive endometrioid cancer, ovarian cancer, cancer, bone development disease

Mutations in the highly conserved Pro-Ser dipeptide repeat of FGFR2 have been identified both in Apert syndrome and in endometrial and ovarian cancers (Wilkie, 1995; Dutt, 2008; Pollock, 2007; Byron, 2010). Missense S252W or P253R mutations affect both the 'b' and 'c' isoforms, although mutation in the FGFR2c isoform is believed to be more clinically relevant to the development of Apert syndrome (Lomri, 1998). In the context of endometrial cancer, these mutations are mutually exclusive with KRAS mutations, but are associated at high frequency with PTEN mutations (Byron, 2008). The S252W and P253R mutations allow the receptor to bind to an expanded range of ligands, such that the mesenchymal splice form (FGFR2c) is anomalously activated by the mesenchymal ligands FGF7 and FGF10, establishing an autocrine signaling loop. These mutations also increase the binding affinity for the receptor's normal epithelial ligands 2- to 8-fold (Yu, 2000; Ibrahimi, 2004b). Based on biochemical and crystal studies, the mutations in the IgII-IgIII linker region are predicted to alter the hydrogen bonding network in this region and may change the conformation and thus the ligand-binding properties of the mutant receptors (Stauber, 2000).

**Followed by:** Autocatalytic phosphorylation of FGFR2c mutants with enhanced ligand binding

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Autocatalytic phosphorylation of FGFR2c mutants with enhanced ligand binding

**Location:** Activated point mutants of FGFR2

**Stable identifier:** R-HSA-2033486

**Type:** transition

**Compartments:** plasma membrane, cytosol

**Diseases:** female reproductive endometrioid cancer, ovarian cancer, cancer, bone development disease

After aberrantly dimerizing in response to mesenchymally expressed ligands, FGFR2c S252W and P253R mutants are assumed to undergo transautophosphorylation analogous to the wild-type receptor, although this has not been explicitly demonstrated. Knock-down or chemical inhibition of other FGFR2-activating mutations identified in endometrial cancer cells has been shown to cause cell death (Byron, 2008).

**Preceded by:** FGFR2c mutants bind an expanded range of ligands

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https://reactome.org
Several missense mutations in the tyrosine kinase domain of FGFR2 have been identified in Crouzon syndrome and similar craniosynostosis disorders (Kan, 2002; Cunningham, 2007). The N549H and K660N mutations are paralogous to FGFR3 N540K and K650N/E mutations identified in hypochondroplasia and thanatophoric dysplasia II (Bellus, 2000). In FGFR3, these mutations have been demonstrated to have weak ligand-independent autophosphorylation and enhanced kinase activity mediated by disruption of a hydrogen-bonding network that holds the receptor in an inactive conformation (Chen, 2007; Bellus, 2000, Raffioni, 1998). Due to the highly conserved nature of these residues across all four FGF receptors, it is generally believed that these germline mutations in FGFR2 are also activating, though this remains to be demonstrated experimentally.

As further support of this notion, activating point mutations in the kinase domain of FGFR2 have also been identified in endometrial, uterine and cervical cancers (Pollock, 2007; Dutt, 2008), and in some cases have been shown to have enhanced kinase activity and to support anchorage-independent growth in NIH 3T3 cells (Dutt, 2008). Knockdown of N549K with short hairpin RNAs or the pan-FGFR inhibitor PD170734 inhibits cell survival in endometrial cancer cell lines, suggesting that FGFR2 activity is required for tumor cell survival (Dutt, 2008; Byron, 2008). Kinase-domain mutants show elevated levels of activity relative to the wild-type even in the absence of receptor phosphorylation, and although their kinase activity is further enhanced upon trans-autophosphorylation, the extent of this is less than that seen in the wild-type, suggesting that the mutant alleles are capable of of supporting ligand-independent activation (Chen, 2007)

Followed by: Autocatalytic phosphorylation of FGFR2 point mutants with enhanced kinase activity

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Autocatalytic phosphorylation of FGFR2 point mutants with enhanced kinase activity

**Location:** Activated point mutants of FGFR2

**Stable identifier:** R-HSA-2033490

**Type:** transition

**Compartments:** plasma membrane, cytosol

**Diseases:** cancer, bone development disease

Several missense mutations in the tyrosine kinase domain of FGFR2 have been identified in Crouzon syndrome and similar craniosynostosis disorders (Kan, 2002; Cunningham, 2007). The N549H and K660N mutations identified in FGFR2 in craniosynostosis disorders are paralogous to FGFR3 N540K and K650N/E mutations identified in hypochondroplasia and thanatophoric dysplasia II (Bellus, 2000). In FGFR3, these mutations have been demonstrated to have weak ligand-independent autophosphorylation and enhanced kinase activity mediated by disruption of a hydrogen-bonding network that holds the receptor in an inactive conformation (Chen, 2007; Bellus, 2000, Raffioni, 1998).

Characterization of FGFR2 proteins containing somatic mutations at these residues support the notion that they have elevated levels of kinase activity. FRS2 is constitutively phosphorylated in the FGFR2 N549K kinase mutant identified in endometrial tumors and knockdown of N549K with short hairpin RNAs or the pan-FGFR inhibitor PD170734 inhibits cell survival in endometrial cancer cells lines, suggesting that FGFR2 activity is required for tumor cell survival. FGFR2 knockdown also results in a significant decrease in the levels of phosphorylated Erk1/2 (Dutt, 2008; Byron, 2008; Pollock, 2007). Crystal structures of FGFR2 kinase mutants N549H and K650N show that the mutations disengage an 'auto-inhibitory brake' on the kinase domain of the receptor. Biochemically, the FGFR2 N549K and K660E mutants show elevated kinase activity relative to the unphosphorylated wild-type protein and have increased activity towards peptide substrates; this activity is stimulated upon receptor phosphorylation, but to a lesser extent than seen with the wild-type receptor (Chen, 2007).

**Preceded by:** Dimerization of FGFR2 point mutants with enhanced kinase activity
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Point mutants of FGFR2 bind and are inactivated by tyrosine kinase inhibitors

**Location:** Activated point mutants of FGFR2

**Stable identifier:** R-HSA-2077424

**Type:** binding

**Compartments:** plasma membrane, cytosol

**Diseases:** cancer

FGFR2 is inhibited by a range of in vitro tyrosine kinase inhibitors, including PD170734 and SU5402 (reviewed in Greulich and Pollock, 2010; Wesche, 2011). In addition, there are a number of FGFR2 inhibitors currently in clinical trials that for treatment of solid malignancies (http://ClinicalTrials.gov).

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