Signaling by FGFR in disease

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23/11/2019
**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: 70

This document contains 5 pathways (see Table of Contents)

https://reactome.org
A number of skeletal and developmental diseases have been shown to arise as a result of mutations in the FGFR1, 2 and 3 genes. These include dwarfism syndromes (achondroplasia, hypochondroplasia and the neonatal lethal disorders thanatophoric dysplasia I and II), as well as craniosynostosis disorders such as Pfeiffer, Apert, Crouzon, Jackson-Weiss and Muenke syndromes (reviewed in Webster and Donoghue 1997; Burke, 1998; Cunningham, 2007; Harada, 2009). These mutations fall into four general regions of the receptor: a) the immunoglobulin (Ig)-like domain II-III linker region, b) the alternatively spliced second half of the Ig III domain, c) the transmembrane domain and d) the tyrosine kinase domain (reviewed in Webster and Donoghue, 1997). With the exception of mutations in class b), which affect only the relevant splice variant, these mutations may be present in either the 'b' or 'c' isoforms. These activating mutations affect FGFR function by altering or expanding the ligand-binding range of the receptors (see for instance Ibrahimi, 2004a), by promoting ligand-independent dimerization (for instance, Galvin, 1996; Neilson and Friesel, 1996; d’Avis, 1998) or by increasing the activity of the kinase domain (for instance, Webster, 1996; Naski, 1996; Tavormina, 1999; Bellus, 2000). Thus, a number of the point mutations found in FGFR receptors alter their activity without altering their intrinsic kinase activity. Many of the mutations that promote constitutive dimerization do so by creating or removing cysteine residues; the presence of an unpaired cysteine in the receptor is believed to promote dimerization through the formation of intramolecular disulphide bonds (Galvin, 1996; Robertson, 1998). Paralogous mutations at equivalent positions have been identified in more than one FGF receptor, sometimes giving rise to different diseases. For instance, mutation of the highly conserved FGFR2 Ser252-Pro253 dipeptide in the region between the second and third Ig domain is responsible for virtually all cases of Apert Syndrome (Wilkie, 1995), while paralogous mutations in FGFR1 (S252R) and FGFR3 (P250R) are associated with Pfeiffer and Crouzon syndromes, respectively (Bellus, 1996). FGFR4 is unique in that mutations of this gene are not known to be associated with any developmental disorders.

Recently, many of the same activating mutations in the FGFR genes that have been characterized in skeletal and developmental disorders have begun to be identified in a range of cancers (reviewed in Turner and Gross, 2010; Greulich and Pollock, 2011; Wesche, 2011). The best established link between a somatic mutation of an FGFR and the development of cancer is in the case of FGFR3, where 50% of bladder cancers have mutations in the FGFR3 coding sequence. Of these mutations, which largely match the activating mutations seen in thanatophoric dysplasias, over half occur at a single residue (S249C) (Capellen, 1999; van Rhijn, 2002). Activating mutations have also been identified in the coding sequences of FGFR1, 2 and 4 (for review, see Wesche, 2011).

In addition to activating point mutations, the FGFR1, 2 and 3 genes are subject to misregulation in cancer through gene amplification and translocation events, which are thought to lead to overexpression and ligand-independent dimerization (Weiss, 2010; Turner, 2010; Kunii, 2008; Takeda, 2007; Chesi, 1997; Avet-Loiseau, 1998; Ronchetti, 2001). It is important to note, however, that in each of these cases, the amplification or translocation involve large genomic regions encompassing additional genes, and the definitive roles of the FGFR genes in promoting oncogenesis has not been totally established. In the case of FGFR-
FR1, translocation events also give rise to FGFR1 fusion proteins that contain the intracellular kinase domain of the receptor fused to a dimerization domain from the partner gene. These fusions, which are expressed in a pre-leukemic myeloproliferative syndrome, dimerize constitutively based on the dimerization domain provided by the fusion partner and are constitutively active (reviewed in Jackson, 2010).

**Literature references**


The FGFR1 gene has been shown to be subject to activating mutations, chromosomal rearrangements and gene amplification leading to a variety of proliferative and developmental disorders depending on whether these events occur in the germline or arise somatically (reviewed in Webster and Donoghue, 1997; Burke, 1998; Cunningham, 2007; Wesche, 2011; Greulich and Pollock, 2011).

Activating mutation P252R in FGFR1 is associated with the development of Pfeiffer syndrome, characterized by craniosynostosis (premature fusion of several sutures in the skull) and broadened thumbs and toes (Muenke, 1994; reviewed in Cunningham, 2007). This residue falls in a highly conserved Pro-Ser dipeptide between the second and third Ig domains of the extracellular region of the receptor. The mutation is thought to increase the number of hydrogen bonds formed with the ligand and to thereby increase ligand-binding affinity (Ibrahimi, 2004a). Unlike other FGF receptors, few activating point mutations in the FGFR1 coding sequence have been identified in cancer. Point mutations in the Ig II-III linker analogous to the P252R Pfeiffer syndrome mutation have been identified in lung cancer and melanoma (Ruhe, 2007; Davies, 2005), and two kinase-domain mutations in FGFR1 have been identified in glioblastoma (Rand, 2005, Network TCGA, 2008).

In contrast, FGFR1 is a target of chromosomal rearrangements in a number of cancers. FGFR1 has been shown to be recurrently translocated in the 8p11 myeloproliferative syndrome (EMS), a pre-leukemic condition also known as stem cell leukemia/lymphoma (SCLL) that rapidly progresses to leukemia. This translocation fuses the kinase domain of FGFR1 with the dimerization domain of one of 10 identified fusion partners, resulting in the constitutive dimerization and activation of the kinase (reviewed in Jackson, 2010).

Amplification of the FGFR1 gene has been implicated as an oncogenic factor in a range of cancers, including breast, ovarian, bladder, lung, oral squamous carcinomas, and rhabdomyosarcoma (reviewed in Turner and Grose, 2010; Wesche, 2011; Greulich and Pollock, 2011), although there are other candidate genes in the amplified region and the definitive role of FGFR1 has not been fully established.

More recently, FGFR1 fusion proteins have been identified in a number of cancers; these are thought to undergo constitutive ligand-independent dimerization and activation based on dimerization motifs found in the fusion partners (reviewed in Parker, 2014).
**Literature references**


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The FGFR2 gene has been shown to be subject to activating mutations and gene amplification leading to a variety of proliferative and developmental disorders depending on whether these events occur in the germline or arise somatically. Activating FGFR2 mutations in the germline give rise to a range of craniosynostotic conditions including Pfeiffer, Apert, Jackson-Weiss, Crouzon and Beare-Stevensen Cutis Gyrata syndromes. These autosomal dominant skeletal disorders are characterized by premature fusion of several sutures in the skull, and in some cases also involve syndactyly (abnormal bone fusions in the hands and feet) (reviewed in Webster and Donoghue, 1997; Burke, 1998; Cunningham, 2007).

Activating FGFR2 mutations arising somatically have been linked to the development of gastric and endometrial cancers (reviewed in Greulich and Pollock, 2011; Wesche, 2011). Many of these mutations are similar or identical to those that contribute to the autosomal disorders described above. Notably, loss-of-function mutations in FGFR2 have also been recently described in melanoma (Gartside, 2009). FGFR2 may also contribute to tumorigenesis through overexpression, as FGFR2 has been identified as a target of gene amplification in gastric and breast cancers (Kunii, 2008; Takeda, 2007).

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[https://reactome.org](https://reactome.org)
The FGFR3 gene has been shown to be subject to activating mutations and gene amplification leading to a variety of proliferative and developmental disorders depending on whether these events occur in the germline or arise somatically.

Activating mutations in FGFR3 are associated with the development of a range of skeletal dysplasias that result in dwarfism (reviewed in Webster and Donoghue, 1997; Burke et al, 1998; Harada et al, 2009). The most common form of human dwarfism is achondroplasia (ACH), which is caused by mutations G380R and G375C in the transmembrane domain of FGFR3 that are thought to promote ligand-independent dimerization (Rousseau et al, 1994; Shiang et al, 1994; Bellus et al, 1995a) Hypochondroplasia (HCH) is a milder form dwarfism that is the result of mutations in the tyrosine kinase domain of FGFR3 (Bellus et al, 1995b). Two neonatal lethal conditions, thanatophoric dysplasia type I and II (TDI and TDII) are also the result of mutations in FGFR3; TDI arises from a range of mutations that either result in the formation of unpaired cysteine residues in the extracellular region that promote aberrant ligand-independent dimerization or by mutations that introduce stop codons (Rousseau et al, 1995; Rousseau et al, 1996, D’Avis et al, 1998). A single mutation, K650E in the second tyrosine kinase domain of FGFR3 is responsible for all identified cases of TDII (Tavormina et al, 1995a, b). Other missense mutations at the same K650 residue give rise to Severe Achondroplasia with Developmental Disorders and Acanthosis Nigricans (SADDAN) syndrome (Tavormina et al, 1999; Bellus et al, 1999). The severity of the phenotype arising from many of the activating FGFR3 mutations has recently been shown to correlate with the extent to which the mutations activate the receptor (Naski et al, 1996; Bellus et al, 2000).

In addition to mutations that cause dwarfism syndromes, a Pro250Arg mutation in the conserved dipeptide between the IgII and IgIII domains has been identified in an atypical craniosynostosis condition (Bellus et al, 1996; Reardon et al, 1997). This mutation, which is paralogous to mutations seen in FGFR1 and 2 in Pfeiffer and Apert Syndrome, respectively, results in an increase in ligand-binding affinity for the receptor (Ibrahim et al, 2004b).

Of all the FGF receptors, FGFR3 has perhaps the best established link to the development in cancer. 50% of bladder cancers have somatic mutations in the coding sequence of FGFR3; of these, more than half occur in the extracellular region at a single position (S249C) (Cappellen et al, 1999; Naski et al, 1996; di Martino et al, 2009, Sibley et al, 2001). Activating mutations are also seen in the juxta- and trans-membrane domains, as well as in the kinase domain (reviewed in Weshe et al, 2011). As is the case for the other receptors, many of the activating mutations that are seen in FGFR3-related cancers mimic the germline FG-
FR3 mutations that give rise to autosomal skeletal disorders and include both ligand-dependent and independent mechanisms (reviewed in Webster and Donoghue, 1997; Burke et al, 1998). In addition to activating mutations, the FGFR3 gene is subject to a translocation event in 15% of multiple myelomas (Avet-Loiseau et al, 1998; Chesi et al, 1997). This chromosomal rearrangement puts the FGFR3 gene under the control of the highly active IGH promoter and promotes overexpression and constitutive activation of FGFR3. In a small proportion of multiple myelomas, the translocation event is accompanied by activating mutations in the FGFR3 coding sequence (Chesi et al, 1997).

More recently, a number of fusion proteins of FGFR3 have been identified in various cancers (Singh et al, 2012; Williams et al, 2013; Parker et al, 2013; Wu et al, 2013; Wang et al, 2014; Yuan et al, 2014; reviewed in Parker et al, 2014). The most common fusion protein is TACC3, a coiled coil protein involved in mitotic spindle assembly. FGFR3 fusion proteins are constitutively active and appear to contribute to proliferation and tumorigenesis through activation of the ERK and AKT signaling pathways (reviewed in Parker et al, 2014).

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FGFR4 is perhaps the least well studied of the FGF receptors, and unlike the case for the other FGFR genes, mutations in FGFR4 are not known to be associated with any developmental disorders. Recently, however, somatically arising mutations in the FGFR4 coding sequence have begun to be identified in some cancers. 8% of rhabdomyosarcomas have activating mutations in the kinase domain of FGFR4. Two of these mutations - N535K (paralogous to the FGFR2 N550K allele found in endometrial cancers) and V550E - have been shown to support the oncogenic transformation of NIH 3T3 cells (Taylor, 2009). An FGFR4 Y367C mutation has also been identified in breast cancers (Ruhe, 2007; Roidl, 2010); mutations of paralogous residues in FGFR2 and FGFR3 are associated with both skeletal dysplasias and the development of diverse cancers (Pollock, 2007; Ruhe, 2007; Rousseau, 1996; Chesi, 1997, 2001).

Finally, a SNP at position 388 of FGFR4 is associated with aggressive disease development. Expression of the G388R allele in breast, colorectal and prostate cancers is correlated with rapid progression times and increased rates of recurrence and metastasis (Bange, 2002; Spinola, 2005; Wang, 2004).

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